DOCTOR OF SCIENCE (DSC)

Collection of research papers (54) published during the period 1961-1976.

Sainsbury, Malcolm

Award date:
1979

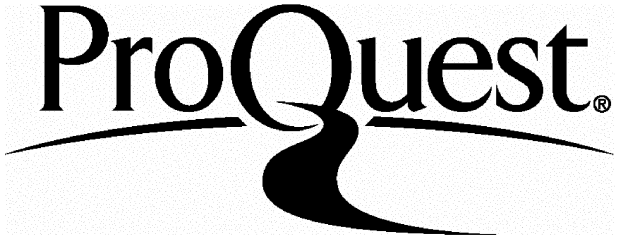
Awarding institution:
University of Bath

Collection of Research Papers (54)

published during the period

1961 - 1976

MALCOLM SAINSBURY



SYNTHESIS OF CAVIUNIN

(J.Org.Chem., 1961, 26, 2453)

180° during 15 min. After cooling to room temperature, the product was taken up in water and washed with chloroform. The aqueous solution was saturated with carbon dioxide and again extracted with chloroform. Upon evaporation of the solvent an oily mass remained which was submitted to vacuum sublimation at 120°, 0.005 mm. Two resublimations yielded colorless crystals of antiarol (IIIb) (5 mg.), m.p. 144–146° (lit.[8] m.p. 145.5–146°). Identity with an authentic sample was established by mixture melting point determination and by infrared spectral comparison; λ_{max} (in Nujol mull) 3.03, 6.16, 12.16, and 12.84 μ.

The degradation product IIIb was treated with boiling acetic anhydride and anhydrous sodium acetate. Crystallization from ethanol afforded colorless prisms of *O*-acetylantiarol, m.p. 73–74° (lit.[19] 74°).

The above aqueous solution was now acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent afforded a crystalline mass which was purified by three vacuum sublimations to yield colorless crystals of homoasaronic acid (IV), melting partially at 78°, resolidifying and melting finally at 84–87° (lit.[16] m.p. 87°). Identity of this product was established as outlined above.

Asaronic acid. A solution of caviunin (Ia) (90 mg.) in 5 ml. of 3% aqueous sodium hydroxide was treated at 50° with small portions of potassium permanganate solution until the consumption of the oxidant subsided. The excess permanganate was reduced with sodium sulfite, the precipitate separated by filtration and washed with 3% sodium hydroxide solution. The combined filtrates were acidified and extracted with chloroform. The organic layer was washed with concentrated sodium bicarbonate solution. This yielded, after acidification and extraction with chloroform, 40 mg. of a slightly yellow solid which was washed with a little ethanol. Vacuum sublimation afforded white crystals of asaronic acid, m.p. 144–145° (lit.[16] m.p. 144–145.5°). Identity with an authentic sample of 2,4,5-trimethoxybenzoic acid was established by mixture melting point determination and infrared spectral comparison; λ_{max} (in Nujol mull), *inter al.*, 5.80, 6.00, 7.77, 8.23, 9.26, and 9.80 μ. Nitration yielded 1-nitro-2,4,5-trimethoxybenzene,[16] m.p. and mixture m.p. with an authentic sample 128–130°.

Oxidation of caviunin (Ia) with alkaline hydrogen peroxide[20] also yielded asaronic acid.

Acknowledgment. The authors wish to record their appreciation of the valuable help afforded by Dr. B. Gilbert. They are indebted to Dr. E. J. Eisenbraun (Stanford University), Dr. W. D. Ollis (Bristol University), and Dr. T. R. Govindachari (Presidency College, Madras) who kindly remitted the model substances. Finally, they wish to thank the Conselho Nacional de Pesquisas, Brazil, for financial aid.

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(19) E. Chapmann, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 3028 (1927).

(20) O. A. Stamm, H. Schmid, and J. Büchi, *Helv. Chim. Acta*, **41**, 2006 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF SCIENCE AND TECHNOLOGY, BRISTOL, AND THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF BRISTOL]

Synthesis of Isoflavones. Part III.[1] Caviunin

S. F. DYKE, W. D. OLLIS, AND M. SAINSBURY

Received September 16, 1960

The synthesis of caviunin (5,7-dihydroxy-2′,4′,5′,6-tetramethoxyisoflavone) using the ethoxalylation method is described.

At the suggestion of Dr. Gottlieb and Dr. Magalhães, whose interest we are pleased to acknowledge, we have investigated the synthesis of caviunin whose determination of structure is described in the preceding paper.[2] Of the various methods which are available for the synthesis of isoflavones,[3] the method due to Baker and Ollis[4] involving the reaction of benzyl *o*-hydroxyphenyl ketones with ethoxalyl chloride is particularly suitable for the synthesis of isoflavones bearing several hydroxyl groups.

Caviunin is one of the more unusual types of isoflavone in that it is a derivative of 5,7-dihydroxy-6-methoxyisoflavone. This class includes tectorigenin (I), irigenin (II), and podospicatin[5] (III) as well as caviunin (IV). Previously the synthesis of isoflavones in this class has presented some difficulty but recently it was shown that the ethoxalylation method could be used for the synthesis of tectorigenin and irigenin.[6] By a similar method, the followed synthesis of caviunin has been achieved.

Hoesch condensation of iretol and 2,4,5-trimethoxybenzyl cyanide yielded the benzyl *o*-hydroxyphenyl ketone (VII). This ketone was treated with ethoxalyl chloride in pyridine solu-

(1) Part II. W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1860 (1953).

(2) O. R. Gottlieb and M. T. Magalhães, *J. Org. Chem.*, 26, 2449 (1961).

(3) W. K. Warburton, *Quart. Revs. (London)*, 8, 67 (1954), K. Venkataraman in L. Zechmeister's *Fortschritte der Chem. Org. Nat.*, Vol. 17, p. 1, Springer Verlag, Wien (1959); W. Baker and W. D. Ollis, *Sci. Proc. Roy. Dublin Soc.*, 27, No. 6, 119 (1956). W. D. Ollis in *The Chemistry of Flavonoids*, ed. by T. A. Geissman (Pergamon Press). In press.

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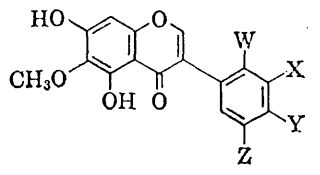
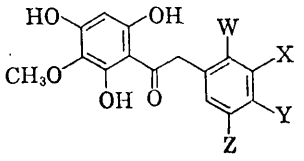
(6) W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert, W. D. Ollis, and R. C. Russell, *Tetrahedron Letters*, No. 5, 6 (1960).

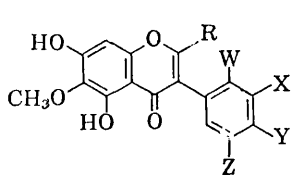


I. W = H; X = H; Y = OH; Z = H
II. W = H; X = OH; Y = OCH_3, Z = OCH_3
III. W = OH; X = H; Y = H; Z = OCH_3
IV. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

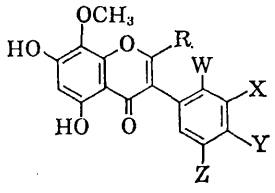


V. W = H; X = H; Y = OH; Z = H
VI. W = H; X = OH; Y = OCH_3; Z = OCH_3
VII. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

tion and the total ethoxalylation product was hydrolyzed with alkali and thermally decarboxylated. The decarboxylation reaction product was purified by chromatography on thick paper and yielded the isoflavone (IV) which was identical with caviunin. The synthetic isoflavone was characterized as its diacetate and both these compounds gave very detailed infrared spectra which were identical with the infrared spectra of caviunin and its diacetate.



VIII



IX

It was expected from our experiences with the synthesis of tectorigenin and irigenin[6] that this synthesis would have yielded both caviunin (VIII. R = X = H; W = Y = Z = OCH_3) and its isomer (IX. R = X = H; W = Y = Z = OCH_3). However, chromatographic examination of the total ethoxalylation product from the ketone (VII) did not indicate that it was a mixture of the two possible products (VIII and IX. R = $CO_2C_2H_5$; X = H; W = Y = Z = OCH_3). Furthermore, the isomer (IX. R = X = H; W = Y = Z = OCH_3) of caviunin was not present in detectable amounts in the total product obtained by hydrolysis and decarboxylation of the crude 2-carbethoxyisoflavone. This result certainly contrasts with our earlier experiences in synthetical approaches to tectorigenin (I) and irigenin (II), when the 2-carbethoxy-Ψ-tectorigenin (IX. R = $CO_2C_2H_5$; W = X = Z = H; Y = OH) and 2-carbethoxy-Ψ-irigenin (IX. R = $CO_2C_2H_5$; W = H; X = OH; Y = Z = OCH_3) were the compounds which were more easily isolated from the mixture produced in the ethoxalylation reaction. Clearly the relative proportions of the two possible products (see VIII and IX. R = $CO_2C_2H_5$) which could be formed from a ketone of the type derived from iretol (see V–VII) are controlled by subtle features.

EXPERIMENTAL

2,4,5-Trimethoxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (VII). A mixture of iretol[7] (4.2 g.), 2,4,5-trimethoxybenzyl cyanide[8] (6.0 g.) and anhydrous zinc chloride (5.0 g.) in anhydrous ether (150 ml.) was saturated with dried hydrogen chloride during 5 hr. at 0° and after keeping at 0° for 1 week, the ether solution was decanted from the oily layer of ketimine hydrochloride–zinc chloride complex which had separated. The oily layer was shaken twice with dry ether (250 ml.) then heated (nitrogen atmosphere) on a steam bath with water (400 ml.) which had been previously boiled with a stream of nitrogen bubbling through it. After cooling and standing, the product was collected and recrystallized from aqueous ethanol giving the ketone (VII) (5.9 g., 60%) as almost colorless rhombs, m.p. 211–212°. The ultraviolet spectrum in 95% ethanol showed a maximum at 291 mμ (log ε 3.39), an inflection at 340 mμ (log ε 2.54) and a minimum at 253 mμ (log ε 2.13).

Anal. Calcd. for $C_{18}H_{20}O_8$: C, 59.46; H, 5.50. Found: C, 59.45; H, 5.79.

Caviunin (IV). The above ketone (VII) (2.48 g.) was dissolved in dry pyridine (50 ml.) and ethoxalyl chloride (4.5 ml.) added with shaking at 0°. After keeping at 0° for 3 days, it was poured into water and extracted with chloroform. The extract was washed with dilute sulfuric acid and with water, dried (magnesium sulfate), and evaporated to yield the 2-carbethoxyisoflavone (3.18 g.) as an oil which showed one main spot (R_f = 0.86) by chromatography[9] on Whatman No. 3 paper.

This oil (3.10 g.) was dissolved in acetone (150 ml.) and added to a mixture of air free water (750 ml.) and 2*N* aqueous sodium hydroxide (33 ml.). After keeping at room temperature for 12 hr., acidification and extraction with chloroform yielded the isoflavone-2-carboxylic acid as a light brown amorphous solid (2.9 g.). Chromatography[9] on Whatman No. 1 paper gave one main spot (R_f 0.79) when examined under ultraviolet light.

A portion (860 mg.) of this crude isoflavone-2-carboxylic acid was divided into 40 small portions (*ca.* 20 mg.). Each small portion was placed in an ignition tube and heated at 295° for 3–3.5 min., when decarboxylation was completed. The product was removed from the ignition tubes with warm ethanol giving a gum (649 mg.) which was chromatographed on silica and eluted with chloroform. The chloroform eluate (438 mg.) was chromatographed[9] on Whatman (No. 3 MM) thick paper and the strip bearing the major band (R_f = 0.75–0.90) was cut out and eluted with ethanol yielding a crystalline compound (222 mg.). This material showed R_f % Asin 0.72 identical with that of caviunin on paper chromatography.[9] Recrystallization of this fraction from chloroform and from ethanol gave caviunin as colorless needles, m.p. and mixed m.p. 191–192°.

Anal. Calcd. for $C_{13}H_6O_4$ $(OCH_3)_4$: C, 60.96; H, 4.65; OCH_3, 33.16. Found: C, 60.46; H, 5.48; OCH_3, 32.67.

(7) R. E. Damschroder and R. L. Shriner, *J. Amer. Chem. Soc.*, 59, 931 (1937).

(8) A. Robertson and G. L. Rusby, *J. Chem. Soc.*, 1371 (1935).

(9) The solvent used in paper chromatography was the top layer of a mixture of benzene, acetic acid, formic acid, and water in the proportions 8:2:1:1 by volume.

The synthetic caviunin was characterized as its diacetate, colorless crystals from ethanol, m.p. and mixed m.p. 197.5°.

Anal. Calcd. for $C_{19}H_{16}O_6$ $(OCH_3)_4$; C, 60.26; H, 4.84; OCH_3, 27.1. Found: C, 59.91; H, 5.18; OCH_3, 28.7.

The natural and synthetic caviunin gave identical infrared (Nujol mull) and ultraviolet spectra. The infrared spectra (Nujol mull) of the diacetates were also identical.

BRISTOL 8, ENGLAND

THE CONSTITUTION OF MUNETONE

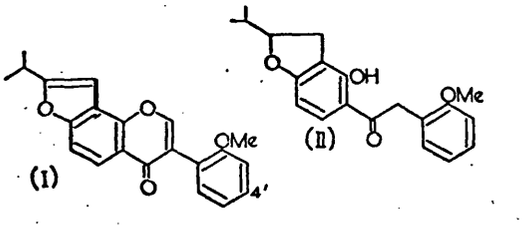
(Proc.Chem.Soc., 1963, 179)

Reprinted from Proceedings of the Chemical Society, June, 1963, page 179

The Constitution of Munetone

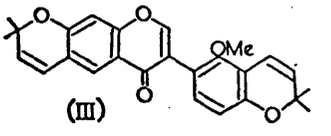
By S. F. Dyke
(Bristol College of Science and Technology),
W. D. Ollis
(The University, Bristol),
and M. F. Sainsbury
(Bristol Technical College)

The isoflavone munetone was originally given the constitution (I),[1] which was unusual in two respects. Like tlatlancuayin,[2] munetone was described as lacking an oxygen-containing substituent in the 4′-position, yet this is frequently present in natural isoflavones;[3] and the structure (I) contained an isoprenoid C_5 residue unique in structural type among natural phenolic compounds.[4] Synthetical studies have now shown that this structure for munetone requires considerable revision.

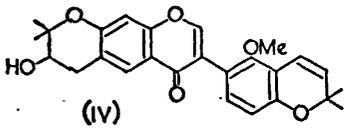


(I)

(II)



(III)



(IV)

The Hoesch reaction[5] of dihydrotubanol[6] with 2-methoxybenzyl cyanide gave the deoxybenzoin (II) which, by reaction with ethyl orthoformate[3,7] followed by dehydrogenation,[8] gave a product of expected structure (I). This material was different from natural munetone, but the nuclear magnetic resonance spectrum of the synthetic isoflavone corresponding to the deoxybenzoin (II) fully supported its structure. The nuclear magnetic resonance spectrum of natural munetone, kindly supplied by Dr. N. L. Dutta, was incompatible with the structure (I) and showed that the formula of munetone should be changed from $C_{21}H_{18}O_4$ to $C_{25}H_{24}O_5$. The 24 protons could then be assigned to two 2,2-dimethylchromen residues,[9] a methoxyl group, an isoflavonoid proton in the 2-position, and two pairs of aromatic protons. One pair of aromatic protons formed an AB system (J 8·5 c./sec.) and the other pair was associated with two singlets slightly broadened by weak coupling (J 0·6 c./sec.). These characteristics and the chemical shifts[10] uniquely define the structure of munetone as (III).

This revised structure (III) for munetone is established by its partial synthesis from mundulone (IV).[11] Mundulone methanesulphonate and ethanolic sodium hydroxide gave a deoxybenzoin identical with munetol,[1] which by reaction with ethyl orthoformate[3,7] gave munetone (III).

(*Received, April 8th*, 1963.)

[1] Dutta, *J. Indian Chem. Soc.*, 1956, **33**, 716; 1959, **36**, 165; 1962, **39**, 475.
[2] Crabbé, Leeming, and Djerassi, *J. Amer. Chem. Soc.*, 1958, **80**, 5258.
[3] Venkataraman, "Fortschritte der Chemie Organischer Naturstoffe," ed. L. Zechmeister, Springer-Verlag, 1959, Vol. XVII, p. 1; Ollis, "The Chemistry of Flavonoid Compounds," ed. T. A. Geissman, Pergamon, Oxford, 1961, p. 353.
[4] Ollis and Sutherland, "Recent Developments in the Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon, Oxford, 1961, p. 74.
[5] Spoerri and Du Bois, *Org. Reactions*, 1949, **5**, 387.
[6] Miyano and Matsui, *Chem. Ber.*, 1959, **92**, 2491.
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[8] Sarin, Sehgal, and Seshadri, *J. Sci. Ind. Res. (India)*, 1957, **16**, *B*, 61.
[9] Burrows, Ollis, and Jackman, *Proc. Chem. Soc.*, 1960, 177.
[10] Dyke, Ollis, and Sainsbury, unpublished work.
[11] Burrows, Finch, Ollis, and Sutherland, *Proc. Chem. Soc.*, 1959, 150.

SYNTHETICAL EVIDENCE CONCERNING THE STRUCTURE OF ICHTHYNONE

(Tetrahedron, 1964, 20, 1331)

Tetrahedron, 1964, Vol. 20, pp. 1331 to 1338. Pergamon Press Ltd. Printed in Northern Ireland

THE EXTRACTIVES OF *PISCIDIA ERYTHRINA* L.—II

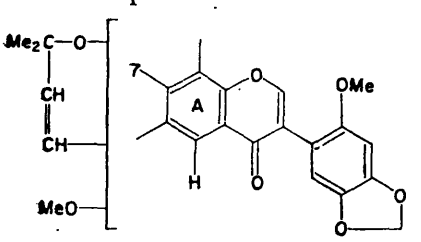
SYNTHETICAL EVIDENCE CONCERNING THE STRUCTURE OF ICHTHYNONE

S. F. DYKE,[a] W. D. OLLIS,[b] M. SAINSBURY[c] and J. S. P. SCHWARZ[d]

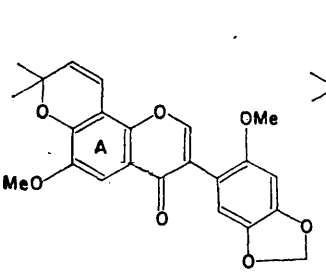
(*Received* 28 *October* 1963)

Abstract—Partial synthesis has shown that a degradation product of ichthynone is the salicylic acid (Vc): this establishes the constitution (II) for ichthynone.

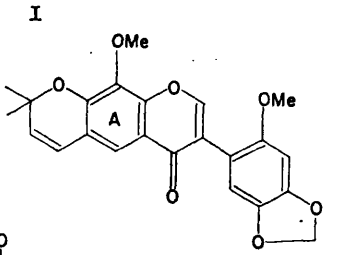
THE preceding paper[1] describes the evidence leading to the derivation of the partial formula (I) for ichthynone and since all the known[2] isoflavones and related isoflavonoids are oxygenated in position 7, structures II or III were strongly preferred for ichthynone on biogenetic grounds. However, further evidence was required to distinguish between these structural possibilities.



I



II



III

Of the two biogenetically acceptable structures II and III considered for ichthynone, the structure II was favoured on two grounds.[1] The dimethoxychroman, $C_{11}H_{12}O(OMe)_{12}$, obtained by the degradation of ichthynone, was not identical with

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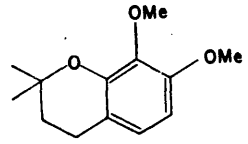
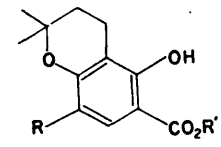
[b] University of Bristol,
[c] Bristol Technical College, Bristol, England.
[d] The Squibb Institute for Medical Research, New Brunswick, N.J., U.S.A.

[1] J. S. Paul Schwarz, Allen I. Cohen, W. D. Ollis, E. A. Kaczka and L. M. Jackman, *Tetrahedron* **20**, 1317 (1964).
[2a] W. K. Warburton, *Quart. Revs.* **8**, 67 (1954).
[2b] K. Venkataraman, *Fortsch. Chem. org. Nat.* **17**, 1 (1959).
[2c] W. D. Ollis, *The Chemistry of Flavonoid Compounds* (Edited by T.A. Geissman), p. 353. Pergamon, Oxford (1961).

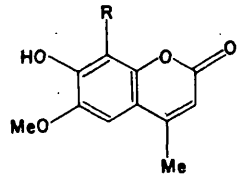
7,8-dimethoxy-2,2-dimethylchromanIV. This clearly excluded structure III, whereas the observation that the UV spectrum of the dimethoxychroman, $C_{11}H_{12}O(OMe)_2$ corresponded to a 1,2,4-trioxygenated benzene chromophore indicated that ichthynone probably had the structure II. If this structural assignment were correct, then it followed that the salicylic acid, $C_{12}H_{13}O_4(OMe)$, obtained[1] from dihydroichthynone (cf. II), would have the structure Vc. This acid was characterized as its methyl ester and this methyl ester (Vd) has now been unambiguously synthesized and shown to be identical with the degradation product of dihydro-ichthynone. This establishes the constitution of ichthynone as the isoflavone (II).



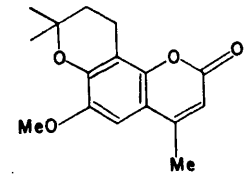
IV



Va R=R'=H
Vb R=OH; R'=H
Vc R=OMe; R'=H
Vd R=OMe; R'=Me



VIa R=H
VIb R=Me_2C=CH−CH_2



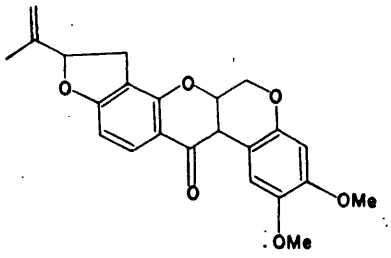
VII

Our initial approaches to the salicylic acid (Vc) involved the synthesis of the coumarin (VII). Reaction[3] of 6-methoxy-7-hydroxy-4-methylcoumarin[4] (VIa) with $\gamma\gamma$-dimethylallyl bromide[5] gave the 8-$\gamma\gamma$-dimethylallyl derivative (VIb) which, by an acid-catalysed cyclization, gave the required coumarin (VII). A number of attempts was made to hydrolyse this coumarin (VII) with alkali, but even under conditions which were successful[6] with closely related compounds, the coumarin (VII) was recovered unchanged. Its stability to alkali recalls similar observations[7] which have been made with other 7-alkoxylated coumarins; it is probably associated with the easy cyclization of the corresponding *o*-hydroxycinnamic acids. In order to try to circumvent this difficulty, various attempts were made to oxidize the coumarin (VII)

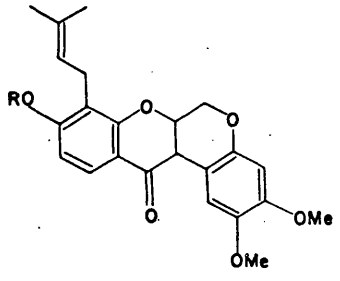
[3] F. A. L. Anet, G. K. Hughes and E. Ritchie, *Austral. J. Sci. Res.* **2**, 608 (1949).
[4] L. Velluz and G. Amiard, *Bull. Soc. Chim.*, Fr. **15**, 1109 (1948).
[5] H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta* **5**, 750 (1962).
[6] *Organic Syntheses* Coll. Vol. III; p. 281. Wiley, New York, (1955).
[7] S. Wawzonek, *Heterocyclic Compounds* (Edited by R. C. Eldderfield), Vol 2; p. 210. Wiley, New York, (1951); D. B. Limaye and K. M. Kulkarni, *Rasayanam* **1**, 208 (1941); *Chem. Abstr.* **36**, 1033 (1942).

directly to the salicylic acid (Vc) with alkaline hydrogen peroxide, but these were unsuccessful.

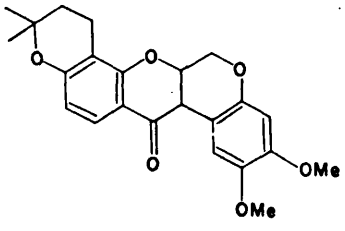
An alternative approach was then considered involving nuclear *p*-hydroxylation of *β*-dihydrotubaic acid (Va) by the Elbs alkaline persulphate method.[8] *β*-Dihydrotubaic acid (Va) has been prepared[9] by the following route. Catalytic hydrogenation of rotenone (VIII) yields rotenonic acid[10] (IXa) which, by acid catalysed cyclization, gives *β*-dihydrorotenone[9] (X). Alkaline cleavage of *β*-dihydrorotenone (X) gives *β*-dihydrotubaic acid (Va).



VIII



IXa R=H
IXb R=Me



X

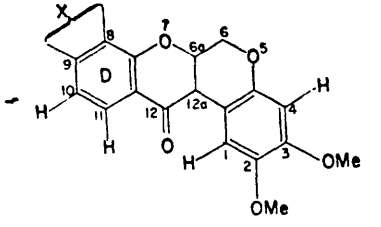
Elbs persulphate oxidation[11] of *β*-dihydrotubaic acid (Va) gave the acid (Vb) which was partially methylated with dimethyl sulphate and potassium carbonate in refluxing benzene to give the methyl ester (Vd). This substance (Vd) was identical with the methyl ester of the salicylic acid, $C_{12}H_{13}O_4(OMe)$, obtained[1] from ichthynone, thus establishing the structure of ichthynone as II.

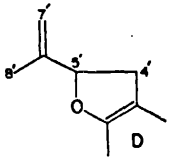
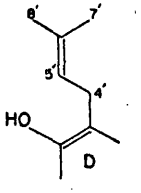
Certain other aspects of this work may now be considered. The formation of rotenonic acid* (IXa) from rotenone (VIII) involves the hydrogenolysis of an allylic ether and it has been assumed[10] that this is associated with migration of the olefinic

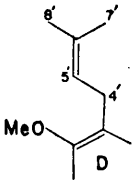
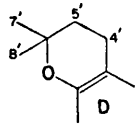
* This name is generally used for this compound although its acidity is due to the *p*-hydroxycarbonyl grouping.[12]

[8] T. R. Seshadri, *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman) p. 175. Pergamon, Oxford (1961).
[9] H. L. Haller, *J. Amer. Chem. Soc.* **53**, 733 (1931).
[10] F. B. LaForge and L. E. Smith, *J. Amer. Chem. Soc.* **51**, 2574 (1929).
[11] S. Rajagopalan, T. R. Seshadri and S. Varadarajan, *Proc. Ind. Acad. Sci.* **30**, 265 (1949).
[12] F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Revs.* **12**, 191 (1933).

CHEMICAL SHIFTS (τ) FOR THE INDICATED PROTONS IN ROTENOIDS



	1-H	4-H	2-OMe and 3-OMe	10-H	11-H	X	Protons in X-residue
Rotenone (VIII)	3·20	3·57	6·23 6·18	3·50 (d, J = 9)	2·13 (d, J = 9)		4′-H, ~6·7 and 7·0, AB of ABX system 5′-H, 4·73 (t, J = 8·5) 7′-H, 4·92 and 5·10, broadened singlets 8′-Me, 8·23
Rotenonic acid (IXa)	3·20	3·53	6·25 6·20	3·47 (d, J = 9)	2·25 (d, J = 9)		4′-H, 6·62 (d, J = 8) 5′-H, ~4·8 (t, J ~ 8) 7′-Me, 8·30 8′-Me, 8·22 OH, 3·53

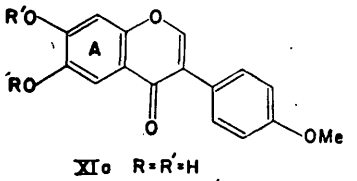
Rotenonic acid methyl ether (IXb)	3·18	3·53	6·23 6·18	3·40 (d, J = 9)	2·13 (d, J = 9)		4'-H, 6·68 (d, J = 8) 5'-H, broad ~4·8 7'-Me, 8·35 8'-Me, 8·22 OMe, 6·13
β-Dihydrorotenone (X)	3·15	3·53	6·22 6·18	3·53 (d, J = 9)	2·25 (d, J = 9)		4'-H, 7·32 (t, J = 6·5) 5'-H, 8·25 (t, J = 6·5) 7'-Me and 8'-Me, 8·65 and 8·70

For abbreviations see Table 1 in preceding paper. The numbering of protons in the X residue is arbitrary and does not conform to nomenclature rules.

bond. Related cleavages *with* rearrangement are known.[13] As the most direct proof of a rearrangement of this type is provided by the NMR spectral characteristics[14] of the $\gamma\gamma$-dimethylallyl group when it is bonded to an aromatic ring, the NMR spectra of rotenonic acid (IXa) and its methyl ether were determined. Some features of the NMR spectra of rotenone and rotenonic acid have been reported previously[15] and are included in the Table as models.

The NMR spectra recorded in the Table are in full accord with their indicated structures. These spectra also show a common complex pattern (τ 5·1–6·5), not indicated in the Table, due to the four protons in positions 6, 6_a, and 12_a, which constitute an ABCD system.[15] The spectra of rotenonic acid and its methyl ether indicate unequivocally the presence of a $\gamma\gamma$-dimethylallyl group[14] and show that the catalytic hydrogenolysis of the allylic ether grouping in rotenone is accompanied by bond migration.[13]

During the early stages of the investigation of the structure of ichthynone, its UV spectrum was misleading, and in this connection 6,7-dihydroxy-4′-methoxyisoflavone (XIa) was synthesized as a model. This isoflavone is not known as a natural product,[2] although its 6-methyl ether, afromosin (XIb), occurs naturally.[16,17] The UV spectra of several related isoflavones are summarized below.



XIa R=R′=H
XIb R=Me, R′=H
XIc R=R′=Me

UV ABSORPTION SPECTRA OF ISOFLAVONES λ_{max} mμ(ε_{max}) in ethanol

6,7-Dihydroxy-4′-methoxyisoflavone (XIa)	231	(24, 550)	258	(33, 110)	326	(13, 490)
Afromosin (XIb)[16]			258	(23, 440)	320	(10, 000)
6,7,4′-Trimethoxyisoflavone (XIc)[16]			261	(50, 120)	320	(19,950)
Ichthynone (II)[1]	232	(33, 600)	262	(24, 300)	309	(14, 100)
					331	(11, 000)
					345	(9, 400)
Dihydroichthynone (cf. II)[1]	233 sh	(24, 400)	256 sh	(15, 700)	312	(18, 700)
Jamaicin (cf. II; 6-OMe = 6-H)[18]	232	(30, 500)	263	(34, 700)	306	(14, 500)

It may be noted that the isoflavones (XIa, XIb, XIc) and ichthynone (II) all exhibit high intensity absorption in the 320–340 mμ region which is not usually regarded as

[13] W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* 77, 2451 (1955); W. G. Dauben, J. S. Paul Schwarz, W. K. Hayes and P. D. Hance, *Ibid.* 82, 2239 (1960).
[14] B. F. Burrows, W. D. Ollis and L. M. Jackman, *Proc. Chem. Soc.* 177 (1960).
[15] L. Crombie and J. W. Lown, *J. Chem. Soc.* 755 (1962).
[16] T. B. H. McMurry and C. Y. Theng, *J. Chem. Soc.* 1491 (1960).
[17] J. B. Harborne, O. R. Gottlieb and M. T. Magalhães, *J. Org. Chem.* 28, 881 (1963).
[18] J. A. Moore and S. Eng. *J. Amer. Chem. Soc.* 78, 395 (1956); A. L. Kapoor, A. Aebi and J. Büchi, *Helv. Chim. Acta* 40, 1574 (1957); O. A. Stamm, H. Schmid and J. Büchi, *Ibid.* 1, 2006 (1958).

being typical of compounds of the isoflavone type.[2,19] The unusual chromophoric characteristics of some of these compounds has been attributed[17] to their 2,4,5-oxygenation pattern of ring A and a similar comment has been made[17] concerning the atypical UV spectrum of 6,7,3′,4′-tetrahydroxyflavanone.[20] The UV spectrum of ichthynone in the 300-350 mμ region is certainly unusual for an isoflavone, but it is doubtful if this should be associated solely with the 2,4,5-oxygenation of its ring A. The isoflavones osajin and pomiferin have a different ring A oxygenation pattern from that of ichthynone, yet they still show long wavelength absorption.[21] In this connection it is probably relevant that ichthynone, osajin and pomiferin all have a chromene system conjugated with ring A. When the chromene double bond is reduced as in dihydroichthynone, then its UV spectrum is more like that of the model isoflavones (XIa, XIb, and XIc). However, it should be noted that the differences between the UV spectra of ichthynone and dihydroichthynone are much greater than the differences between jamaicin and dihydrojamaicin. It is clear that conjugation involving chromene double bonds may be associated with unexpectedly large bathochromic shifts and that comparison of the corresponding chromans with models may be more directly informative in such cases.

EXPERIMENTAL

M.ps are uncorrected.

8-(γγ-Dimethylallyl)-7-hydroxy-6-methoxy-4-methylcoumarin (VIb). A solution of NaOH (300 mg) in water (2 ml) was added at 0° to a vigorously stirred solution of 7-hydroxy-6-methoxy-4-methylcoumarin[4] (1 g) in acetone (25 ml). After 20 min the yellow precipitate was collected, dried over phosphoric anhydride (24 hr), then suspended in anhydrous benzene (25 ml), and heated under reflux with γγ-dimethylallyl bromide (3 ml). The benzene was removed under diminished press. and the residue was treated with dil. acid and extracted with chloroform. This extract after washing with 2N NaOH yielded 8-(*γγ-dimethylallyl*)-7-*hydroxy*-6-*methoxy*-4-*methylcoumarin* (620 mg, 47%) as colourless needles, m.p. 179–180° from ethanol, ν_{max} (nujol) 3320, 1718, and 1618 cm^{-1}, λ_{max} (ethanol) 216 mμ (ε 15,970), 232 mμ (ε 15,320), 300 mμ sh (ε 4,610), 344 mμ (ε 12,460). (Found: C, 70·27; H, 6·86. $C_{16}H_{18}O_4$ requires: C, 70·05; H, 6·61%).

7,8-(2′,2′-Dimethylchromano)-6-methoxy-4-methylcoumarin (VII). A solution of 8-(γγ-dimethylallyl)-7-hydroxy-6-methoxy-4-methylcoumarin (100 mg) in glacial acetic acid (5 ml) and conc. HCl (0·25 ml) was heated under reflux for 3 hr and the residue obtained by evaporation under diminished press. crystallized from aqueous ethanol giving 7,8-(2′,2′-*dimethylchromano*)-6-*methoxy*-4-*methylcoumarin* (82 mg; 82%) as pale yellow prisms, m.p. 201–202°, ν_{max} (nujol) 1710 and 1610 cm^{-1}, λ_{max} (ethanol) 212 mμ (ε 29,450), 231·mμ (ε 16,970), 310 mμ sh (ε 3,770), 347 mμ (ε 10,960). (Found: C, 70·24; H, 6·64. $C_{16}H_{18}O_4$ requires: C, 70·05; H, 6·61%).

Rotenonic acid methyl ether (IXb). Dimethyl sulphate (4 ml) was added during 1 hr to a vigorously stirred mixture of rotenonic acid (IXa; 14 g), anhydrous potassium carbonate (40 g), and acetone (100 ml) which was heated under reflux. After a further 2 hr, the mixture was cooled, water (500 ml) was added, and chloroform extraction yielded a product (13·46 g) which was chromatographed on silica using benzene as solvent. This yielded rotenonic acid methyl ether (7 g) as colourless prisms, m.p. 142°, from methanol. (Found: C, 70·6; H, 6·6; OMe, 21·5. $C_{21}H_{17}O_3(OMe)_3$ requires: C, 70.2; H, 6·3; OMe, 22·7%).

5,8-Dihydroxy-2,2-dimethylchroman-6-carboxylic acid (Vb). β-Dihydrotubaic acid, m.p. 175–176°, ν_{max} (nujol) 3195, 1665, 1629 cm^{-1}, λ_{max} (ethanol) 263 mμ (ε 14,650), 297 m (μ 5,180) was prepared from β-dihydrorotenone (X) *via* rotenonic acid (IXa) as described by Haller.[9]

A solution of potassium persulphate (950 mg) in water (15 ml) was added during 4 hr at 10° to a stirred solution of β-dihydrotubaic acid (Va; 800 mg) in 8% NaOH aq. (10 ml). After a further

[19] L. Jurd, *The Chemistry of Flavonoid Compounds*, (Edited by T. A. Geissman) p. 107. Pergamon, Oxford (1961).

[20] J. B. Harborne and T. A. Geissman, *J. Amer. Chem. Soc.* **78**, 329 (1956).

[21] Ref. 2c, p. 367.

24 hr at room temp, the mixture was neutralized with dil. HCl and extracted with ether. Conc. HCl (6 ml) and Na_2SO_3 (1 g) were added to the aqueous phase and after heating (100°) for 30 min, cooling and ether extraction yielded a crystalline product (240 mg). Recrystallization from aqueous ethanol gave 5,8-*dihydroxy*-2,2-*dimethylchroman*-6-*carboxylic acid* (160 mg; 19%) as colourless needles, m.p. 179°; it gave a green-brown coloration with ethanolic ferric chloride, ν_{max} (nujol) 3535, 3498, ~3210, 1668, and 1628 cm^{-1}, λ_{max} (ethanol) 213 mμ(ε 18,900), 225 mμ sh (ε 12,160), 267 mμ (ε 9,095), 323 mμ (ε 5,380). (Found: C, 60·32; H, 6·14. $C_{12}H_{14}O_5$ requires: C, 60·50; H, 5·92%).

6-*Carbomethoxy*-5-*hydroxy*-8-*methoxy*-2,2-*dimethylchroman* (Vd). A mixture of 5,8-dihydroxy-2,2-dimethylchroman-6-carboxylic acid (130 mg), anhydrous potassium carbonate (500 mg), dimethyl sulphate (0·11 ml), and anhydrous benzene (5 ml) was heated under reflux for 4 hr, cooled, ether added, and the solid removed. The filtrate yielded a solid which was recrystallized from light petroleum (b.p. 40–60°) giving 6-*carbomethoxy*-5-*hydroxy*-8-*methoxy*-2,2-*dimethylchroman* (42 mg; 28%) as colourless prisms, m.p. 111°; it gave intense blue-green coloration with ethanolic ferric chloride, ν_{max} (chloroform) ~3200, 1665, 1628 cm^{-1}, λ_{max} (ethanol) 213 mμ (ε 21,580), 230 mμ sh (ε 14,520), 270 mμ (ε 13,430), 320 mμ (ε 6,950). (Found: C, 63·33; H, 6·87; OMe, 22·62. Calc. for $C_{12}H_{12}O_3(OMe)_2$: C, 63·14; H, 6·81; OMe, 23·31%).

This ester was identical (mixed m.p., IR and NMR spectra) with one of the degradation products of dihydroichthynone (see preceding paper).

4-*Methoxybenzenyl*-2,4,5-*trihydroxyphenyl ketone*. 1, 2, 4-Trihydroxybenzene (13·0 g), *p*-methoxybenzyl cyanide (15·2 g), and powdered zinc chloride (15·0 g) were suspended in anhydrous ether and saturated with hydrogen chloride at 0° for 5 hr. The mixture was stored at 0° for 1 week, and then the supernatant liquid was decanted from the heavy red oil which had separated. This oil was washed with dry ether (2 × 250 ml), then water (450 ml) and conc. HCl (10 ml) were added and the mixture heated (2 hr) on a steam bath under a N_2 atmosphere. After cooling, the crystalline product was collected and recrystallized from aqueous ethanol giving 4-*methoxybenzyl*-2,4,5-*trihydroxyphenyl ketone* (10·3 g; 36%) as straw-coloured needles, m.p. 181·5–182·5°, ν_{max} (nujol) ~3300 and 1650 cm^{-1}, λ_{max} (ethanol) 219 μ (ε 20,420), 244 mμ (ε 12,020), 283 mμ (ε 12,300), 354 mμ (ε 7,940). (Found: C, 65·52; H, 5·24; OMe, 11·25. $C_{14}H_{11}O_3(OMe)$ requires: C, 65·75; H, 5·43; OMe, 11·30%).

Methylation of this ketone using dimethyl sulphate and potassium carbonate in acetone gave the known 4-methobenzyl-2,4,5-trimethoxyphenyl ketone, m.p. 87°[16] (Found: C, 68·01; H, 6·39; OMe, 38·4. Calc. for $C_{14}H_8O(OMe)_4$: C, 68·30; H, 6·40; OMe, 39·2%).

2-*Carbethoxy*-6,7-*dihydroxy*-4′-*methoxyisoflavone*. Ethoxalyl chloride (16·0 g) was added dropwise at 0° during 1 hr to a stirred solution of 4-methoxybenzyl-2,4,5,trihydroxyphenyl ketone (7·65 g) in anhydrous pyridine (60 ml). The mixture was stored at 0° for 60 hr, poured into water, and extracted with chloroform. This extract, after shaking with 2N HCl, yielded 2-carbethoxy-6,7-dihydroxy-4′-methoxyisoflavone (9·48 g; 90%) as pale yellow prisms, m.p. 237–238°, from aqueous methanol, λ_{max} (ethanol) 215 mμ (ε 12,590), 240 mμ (ε 9,120), 341 mμ (ε 38,000). (Found: C, 63·82; H, 4·63. $C_{19}H_{16}O_7$ requires: C, 64·0; H, 4·50%).

6,7-*Dihydroxy*-4′-*methoxyisoflavone* (XIa). The preceding ester (7·79 g) was dissolved in acetone (100 ml), water (1500 ml), and 2N NaOH (75 ml), and after standing at room temp under a N_2 atmosphere for 12 hr, 2N H_2SO_4 was added and the precipitated acid (6·31 g; 88%) collected.

This acid (2·0 g) was decarboxylated in portions (25 mg) by heating it in small ignition tubes in a Wood's metal bath (280–285°) for 2·5 min. The tubes were then extracted with hot ethanol and concentration followed by recrystallization from ethanol gave 6,7-*dihydroxy*-4′-*methoxyisoflavone* (1·30 g; 78%) as pale brown prisms, m.p. 291·5–192·5° (dec), ν_{max} (nujol) 3505, 3150, and 1632 cm^{-1} λ_{max} (ethanol) 231 mμ (ε 24,550), 258 mμ (ε 32,110), 326 mμ (ε 13,490). (Found: C, 67·47; H, 4·23; OMe, 10·94. $C_{15}H_9O_4(OMe)$ requires: C, 67·75; H, 4·39; OMe, 10·91%).

Methylation of this isoflavone gave the known 6,7,4′-trimethoxy-isoflavone, m.p. 174–175°.[16]

1,2-DIHYDROISOQUINOLINE REARRANGEMENTS

(Tetrahedron Letters, 1964, 1545)

Tetrahedron Letters No.24, pp. 1545-1548, 1964. Pergamon Press Ltd.
Printed in Great Britain.

1,2-DIHYDROISOQUINOLINE REARRANGEMENTS

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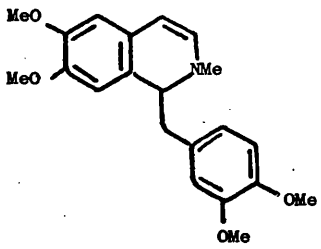
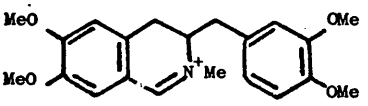
Bristol, England
b) Bristol Technical College, Bristol, England.

(Received 27 April 1964)

Knabe and Kubitz have shown recently[1,2] that mild acid treatment of 2-methyl-1,2-dihydropapaverine (1) results in the formation, in 70% yield, of the 2-methyl-3-(3',4'-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (2).



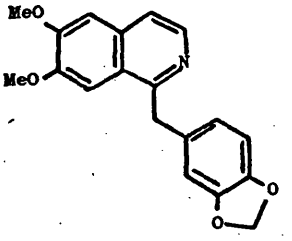
(1)



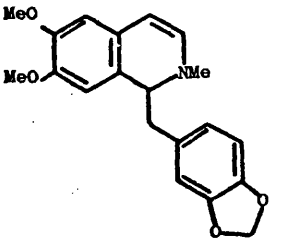
(2)

It became of interest to us to study the action of dilute acids on a 1-benzylisoquinoline derivative, whose aromatic rings were unsymmetrically substituted.

1-(3',4'-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline (3), (m.p. 123°, lit.[3] 123°) was synthesised by the standard[4] Bischler-Napieralski ring-closure of the corresponding amide, followed by dehydrogenation of the intermediate 3,4—dihydroisoquinoline[5] (m.p. 108°).

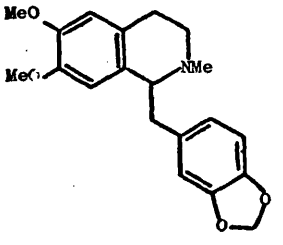


(3)

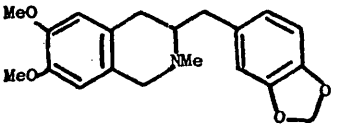


(4)

The methiodide of (3) (m.p. 232°) was reduced, in tetrahydrofuran solution, with lithium aluminium hydride, essentially as described previously[6]; the resulting 1,2-dihydroisoquinoline (4) ($\lambda_{max.}$ at 215, 255, 290 and 335 mμ) was, without delay, warmed with 2N hydrochloric acid as described by Knabe and Kubitz[2,7]. An intense red-violet colour developed, which very quickly faded to yellow. Basification and extraction with chloroform then yielded an oil ($\lambda_{max.}$ at 214, 245, 290, 315 and 368 mμ), which was reduced immediately with sodium borohydride in ethanol. The product (m.p. 170°, methiodide monohydrate 155-158° dec.) was different from authentic[8] 1-(3',4'-methylenedioxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5) (m.p. 122°, methiodidemonohydrate m.p. 215-216°), and was shown to be 2-methyl-3-(3',4'-methylenedioxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6) by Hofmann degradation.

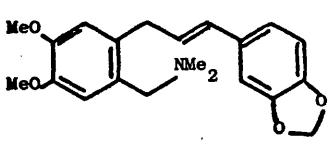


(5)

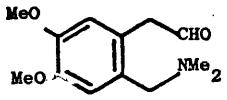


(6)

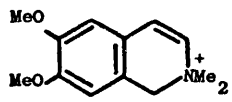
From the ozonolysis of the styrenoid methine base (7) ($\lambda_{max.}$ at 271 and 292 mμ) piperonal (80%) was isolated. The nitrogen-containing fragment (8) was very unstable, presumably due to cyclisation to, and decomposition of the 1,2-dihydroisoquinoline (9).



(7)

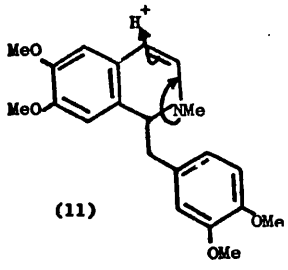


(8)

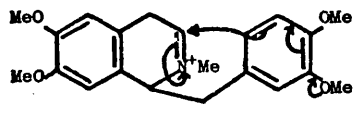


(9)

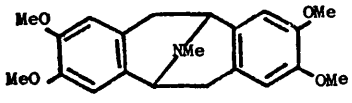
It is remarkable that of the β-hydrogen atoms available in the transition state of the Hofmann degradation of (6), it is one of those of the exocyclic benzyl group which is preferred. The generally accepted mechanism for the conversion of 2-methyl-1,2-dihydropapaverine (11) to N-methylpavine[6,9], which is brought about by concentrated acids, involves the protonated form (12) of (11). This is then susceptible to nucleophilic attack as shown.



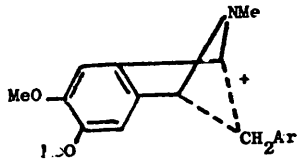
(11)



(12)

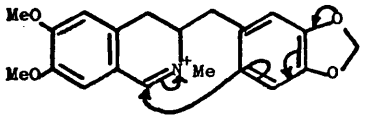


(13)

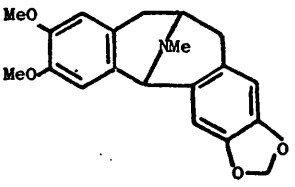


(14)

In the benzyl-migration reaction it is possible that the intermediate of type (12) reacts as (14), and the reaction may therefore be reversible. However treatment of the 3-benzyl derivative (15) with dilute mineral acids led only to recovered starting material. It is also possible that a pavine-like structure (16) could arise from (15), but once again only starting material was recovered when (15) was heated with a mixture of formic and phosphoric acids under the conditions[9] whereby (11) was converted into (13).



(15)



(16)

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1. J. Knabe, J. Kubitz and N. Ruppenthal, Angew.Chem., International edition, 2, 689 (1963). Ger. edition 75, 981 (1963).
2. J. Knabe and J. Kubitz, Arch. Pharm., 297, 129 (1964).
3. C. Mannich and O. Walther, Arch. Pharm., 265, 1 (1927).
4. W. M. Whaley and T. R. Govindachari, Organic Reactions, Vol.VI, p.74, J. Wiley (1957).
5. Satisfactory analyses were obtained for all compounds reported in this communication.
6. A. R. Battersby, D. J. Le Count, J. Garratt and R. I. Thrift, Tetrahedron, 14, 46 (1961).
7. J. Knabe, - private communication.
8. Z. Kitasato and H.Shishido, Ann, 527, 176 (1937).
9. A. R. Battersby and R. Binks, J. Chem. Soc., 2888 (1955).

1,2-DIHYDROISOQUINOLINES - REARRANGEMENT I

(Tetrahedron, 1965, 21, 1907)

Tetrahedron, 1965, Vol. 21, pp. 1907 to 1915. Pergamon Press Ltd. Printed in Northern Ireland

1,2-DIHYDROISOQUINOLINES—I

REARRANGEMENT[1]

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Department of Chemistry, College of Science and Technology, Bristol.

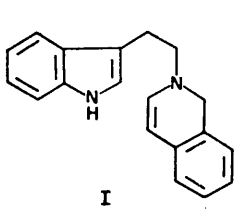
(*Received* 16 *February* 1965)

Abstract—1-(3,4-Methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline has been shown to rearrange to 3-(3,4-methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium chloride when treated with 2% hydrochloric acid.

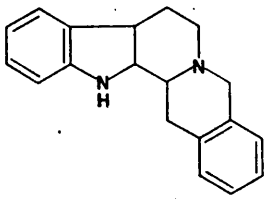
1,2-DIHYDROISOQUINOLINES have been obtained from isoquinolinium salts by reduction with sodium dithionite,[2] LAH[3] or dialkyl aluminium hydrides,[4] or by the reaction with Grignard reagents[5] (to yield 1-substituted derivatives). Various other methods have also been described.[6] There are several reports describing the instability of 1,2-dihydroisoquinolines, especially in the presence of air,[3,7] but compounds such as 1-hydroxy-2-cyano-1,2-dihydroisoquinoline are quite stable,[8] as are the dihydroberberines; a phenyl group in the 3-position seems to confer stability upon a 1,2-dihydroisoquinoline, and 1-phenyl-1,2-dihydroisoquinoline is quite stable to acids (in the absence of air).[9–11]

Interest in 1,2-dihydroisoquinolines has been revived recently firstly, by the observation[12] that derivatives such as (I) are readily cyclized to (II) and secondly, that pavine (VI), a product isolated[13] from the reduction of papaverine (III), with tin and

[1] A Preliminary account has been published: S. F. Dyke and M. Sainsbury, *Tetrahedron Letters* 1545 (1964).
[2] P. Karrer, *Helv. Chim. Acta* **21**, 223 (1938).
[3] For example [a] H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949);
[b] T. Kametani and K. Fukumoto, Yakugaku Zasshi, 80, 1288 (1960); *Chem. Abstr.* **55**, 3589f (1961).
[4] W. P. Newmann, *Angew. Chem.* 70, 401 (1958).
[5] W. Bradley and S. Jeffrey, *J. Chem. Soc.* 2770 (1954).
[6] J. Gademer, M. Oberlin and A. Schoeler, *Arch. Pharm.* **263**, 81 (1925).
[7] T. Kametani, K. Kukumoto and T. Katagi, *Chem. Pharm. Bull.* **7**, 567 (1959); J. Hagimiwa, I Murakoshi and Y. Ohe, *Yakugaku Zasshi* 79, 1578 (1959).
[8] M. D. Johnson, *J. Chem. Soc.* 200 (1964).
[9] M. Freund and C. Bode, *Ber. Dtsch. Chem. Ges.* **42**, 1746 (1909).
[10] P. R. Brook and P. Karrer, *Helv. Chim. Acta* 40, 260 (1957).
[11] S. F. Dyke and M. Sainsbury, unpublished work.
[12a] P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949);
[b] J. W. Huffman, *Ibid.* 80, 5193 (1958);
[c] E. Wenkert, R. A. Massy-Westropp and R. G. Lewis, *Ibid.* **84**, 3732 (1962);
[d] K. T. Potts and R. Robinson, *J. Chem. Soc.* 2675 (1955);
[e] D. R. Liljegren and K. T. Potts, *J. Org. Chem.* **27**, 377 (1962);
[f] K. T. Potts and D. R. Liljegren, *Ibid.* **28**, 3066, 3202 (1963);
[g] B. Belleau, *Chem. & Ind.* 229 (1955);
[h] R. C. Elderfield and B. A. Fisher, *J. Org. Chem.* **23**, 332 (1958).
[13a] F. L. Pyman, *J. Chem. Soc.* 95, 1610 (1909);
[b] F. L. Pyman and W. C. Reynolds, *J. Chem. Soc.* 97, 1320 (1910).

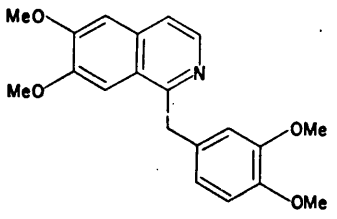


I

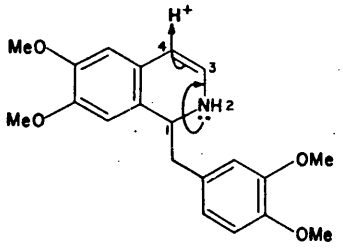


II

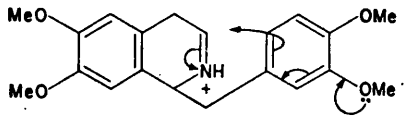
hydrochloric acid, can be regarded[14] as being formed by protonation and ring-closure of the intermediate reduction product, 1,2-dihydropapaverine (IV), as shown in IV → VI. The parent ring system was later obtained[15] by the cyclization of 1-benzyl-2-methyl-1,2-dihydroisoquinoline with phosphoric acid. As pointed out by Battersby,[14] 1,2-dihydroisoquinolines should be susceptible to electrophilic attack at C_4 and to nucleophilic attack at C_3. The former type of reaction is closely related to the known[16] alkylation of enamines by alkyl halides, and is illustrated by the synthesis[17] of corydaline (X) from palmatine (VII) via (VIII) and (IX), and by the reductive condensation of isoquinoline methiodide and benzaldehyde[18] to 2-methyl-4-benzyl-1,2,3,4-tetrahydroisoquinoline. Nucleophilic attack at C_3 of a 1,2-dihydroisoquinoline,



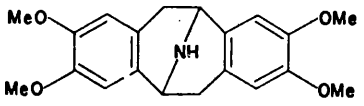
III



IV

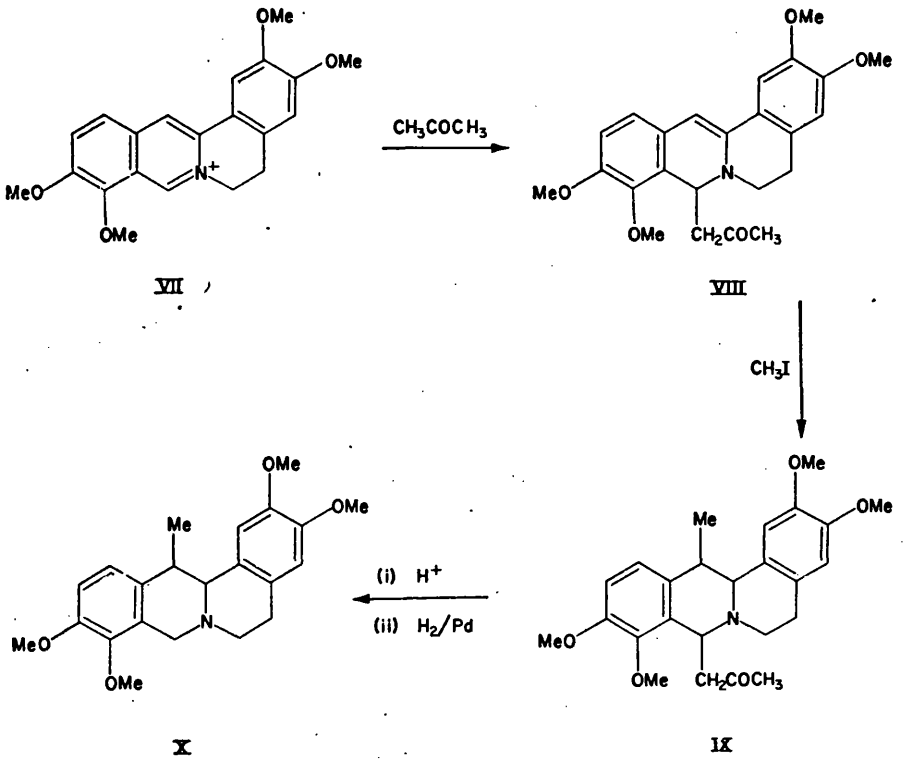


V

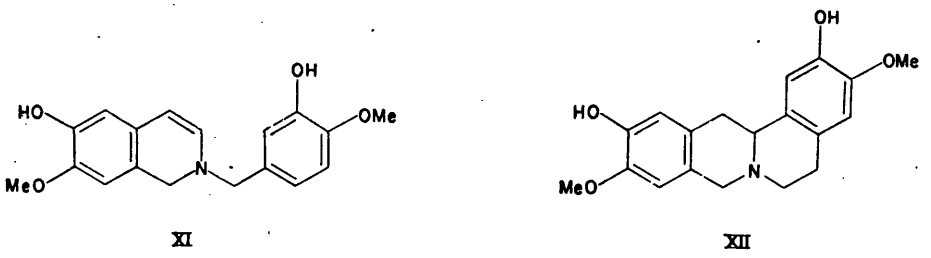


VI

[14] A. R. Battersby and R. Binks, *J. Chem. Soc.* 2888 (1955).
[15] C. Wittig, H. Tenhaeff, W. Schoch and C. Koenig, *Liebigs Ann.* **1**, 572 (1951).
[16a] E. E. P. Hamilton and R. Robinson, *J. Chem. Soc.* **109**, 1029 (1916);
[b] R. Robinson, *Ibid.* **109**, 1038 (1916);
[c] R. Robinson and J. E. Saxton, *Ibid.* 976 (1962);
[d] C. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Amer. Chem. Soc.* **85**, 207 (1963);
[e] J. Szmuszkovicz, *Advances in Organic Chemistry, Methods and results* Vol. 4; p. 1. Interscience, New York (1963).
[17] F. Bruckhausen, *Arch. Pharm.* **261**, 28 (1922).
[18] R. Grewe, W. Kruger and E. Vandernidin, *Chem. Ber.* **97**, 120 (1964).



illustrated by the formation of pavine, has been extended[19] to the synthesis of (±)-coreximine (XII) by treating the corresponding 1,2-dihydroisoquinoline (XI) with concentrated acids, and other examples of the synthesis of the protoberberine ring system have been described.[20] A closely related ring-closure of an N-phenylethyl-

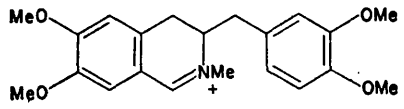


isocarbostyril has also been observed.[20] More recently a new reaction of 1,2-dihydroisoquinolines was uncovered,[21] when it was found that treatment of 2-methyl-1,2-dihydropapaverine with acids under very mild conditions caused rearrangement to

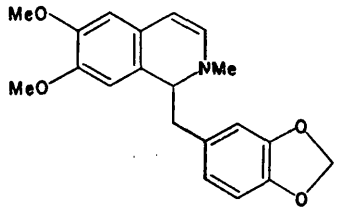
[19] A. R. Battersby, D. J. Le Count, S. Garratt and R. I. Thrift, *Tetrahedron* **14**, 46 (1961).
[20a] J. W. Huffman and E. C. Miller, *J. Org. Chem.* **25**, 90 (1960);
[b] D. W. Brown and S. F. Dyke *Tetrahedron Letters* 3587 (1964).
[21a] J. Knabe and J. Kubitz, *Angew. Chem.* (Int. Ed.) **2**, 689 (1963); German Version **75**, 981 (1963);
[b] *Arch. Pharm.* **297**, 129 (1964);
[c] J. Knabe and N. Ruppenthal, *Ibid.* **297**, 141, 268 (1964).

the 2-methyl-3-(3,4-dimethoxy)benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (XIII).

It was of interest to us to study the action of dilute acids upon a 1-benzyl-1,2-dihydroisoquinoline whose aromatic rings are unsymmetrically substituted, and we selected the derivative (XIV). 1-(3,4-Methylenedioxy)benzyl-6,7-dimethoxyisoquinoline has been prepared[23] by the action of phosphorus oxychloride upon the trimethoxy compound (XV); yields of the order of 40% were claimed, but in our hands the yield never exceeded 8%. A more satisfactory method involved the standard[24] Bischler-Napieralski ring-closure to the 3,4-dihydroisoquinoline (XVI, R = H), followed by catalytic dehydrogenation. Reduction of the isoquinoline methiodide with LAH in boiling ether, or in tetrahydrofuran at room temperature, yielded (XIV) as in oil, whose UV spectrum (qualitative) exhibited maxima at 215, 255, 290 and 335 mμ, in close agreement with the reports of previous workers[19] for 1,2-dihydroisoquinolines. This substance was, without purification, and without delay, warmed with 2% aqueous hydrochloric acid as described by Knabe and Kubitz[21,22]; the initially deep wine-coloured solution rapidly changed to bright yellow. Neutralization of the solution and extraction with ether gave a tertiary base which proved to be identical with 1-(3,4-methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVII), obtained by the reduction of XVI, (R = Me) with sodium borohydride. No



XIII



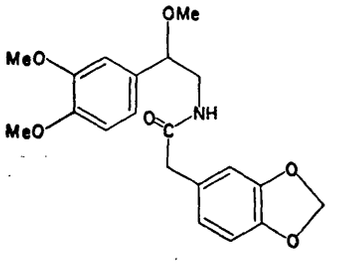
XIV

trace of the N-methylpavine type of structure could be found. It has always been assumed that reduction of isoquinolinium salts by LAH does not proceed beyond the 1,2-dihydroisoquinoline stage, but we have been able to show, by the use of thin film chromatography, that the crude reduction product (XIV) is contaminated with a small amount of XVII, the amount increasing with increasing reaction time. The quaternary salt (XVIII), whose UV spectrum was typical of that of a 3,4-dihydroisoquinolinium salt, was isolated from the neutral aqueous layer either as the pseudobase by extraction with chloroform, or as the pseudocyanide (m.p. 129°) by precipitation with potassium cyanide. Reduction of XVIII with $NaBH_4$ yielded the tetrahydroisoquinoline (XIX), the structure of which rests upon the following evidence. The pseudocyanide m.p. 129° was shown by mixed m.p. determination to be different from the pseudocyanide (m.p. 134°) of the authentic 3,4-dihydroisoquinolinium salt (XVI,

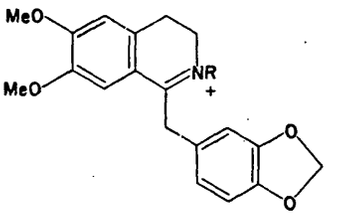
[22] We are indebted to Prof. Knabe for disclosing the experimental details before publication of his work.

[23] C. Mannich and O. Walter, *Arch. Pharm.* 265, 1 (1927).

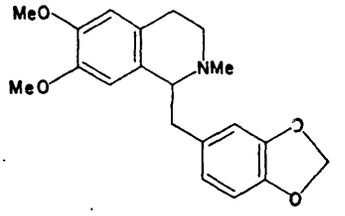
[24] W. M. Whaley and T. R. Govindachari, *Org. Reactions* Vol. VI, p. 74. J. Wiley, New York (1957).



XV

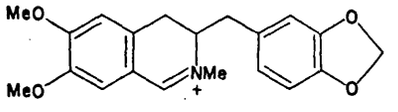


XVI

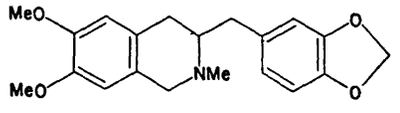


XVII

$R = CH_3$) (the IR spectra of these two pseudocyanides are similar, and the spectra of XVII and XIX are almost identical). Hofmann degradation of XIX yielded a styrenoid methine base formulated as XX, with the double bond in conjugation with the methylenedioxybenzene nucleus, since ozonolysis gave piperonal (80% yield) as the only neutral aldehyde fragment. The expected amino-aldehyde (XXI) was very



XVIII

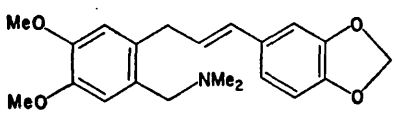


XIX

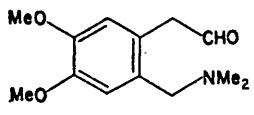
unstable, presumably due to cyclization to, and decomposition of the 1,2-dihydroisoquinoline (XXII).

Gensler *et al.*[25] have shown that 3,4-dihydroisoquinolines, for example XXIII, can be degraded to styrenoid aldehydes such as XXIV by treatment with alkaline dimethyl sulphate; 1-substituted 3,4-dihydroisoquinolines yield styrenoid ketones. When this method was applied to XVIII, a nitrogen-free oil was obtained, which was shown by thin-layer chromatography to be a mixture (presumably of double bond isomers) of two very similar substances. Crystallization of the major component from methanol afforded a pale yellow solid, m.p. 115°. The NMR spectrum (Fig. 1) is entirely in accord with structure XXV. The aldehyde stretching frequency appears at 1675 cm^{-1}

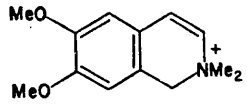
[25] W. J. Gensler, E. M. Healy, I. Unshuus and A. L. Bluhm., *J. Amer. Chem. Soc.* **78**, 1713 (1956).



XX

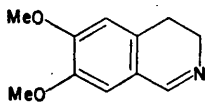


XXI

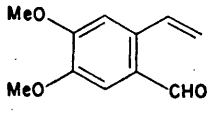


XXII

in the IR spectrum; the aldehyde (XXIV) also exhibits a band at 1675 cm^{-1}, and this shift to lower frequencies is presumably due to the influence of the styrenoid double bond in the *ortho* position. Oxidation of XXV with potassium permanganate caused extensive degradation but the presence of small amounts of piperonylic acid and

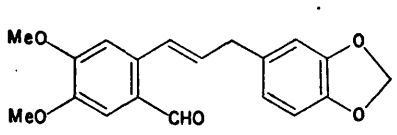


XXIII



XXIV

m-hemipinic acid was demonstrated chromatographically. Ozonolysis of XXV, followed by oxidation with silver oxide gave, ultimately, *m*-hemipinic acid, and the presence of some homopiperonylic acid was indicated by thin layer chromatography.

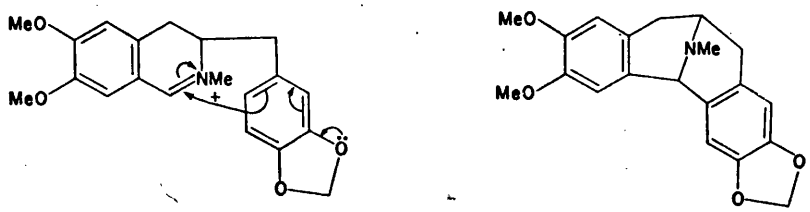


XXV

XXVI

Our evidence agrees completely with the conclusions of Knabe and Kubitz,[21] and the reaction clearly involves the migration of the benzyl group from C_1 to C_3 of the isoquinoline ring, most probably through an intermediate such as XXVI. Knabe[26] independently suggested the same mechanism, also suggesting that it is of the type[27] "allyl rearrangement with internal return." It might be anticipated that the reaction should be reversible, but treatment of XVIII with dilute mineral acids led only to recovered starting material. The possibility also exists that a pavine-type structure

[26] J. Knabe, private communication; J. Knabe and N. Ruppenthal, *Naturwiss.* **51**, 482 (1964).
[27] W. C. Young, S. Winstein and H. L. Goering, *J. Amer. Chem. Soc.* **73**, 1958 (1951).



XXVII XXVIII

XXVIII may arise as shown in XXVII → XXVIII, but once again starting material was recovered when XVIII ≡ XXVII was heated with a mixture of formic acid and phosphoric acid under the conditions[14] whereby 2-methyl-1,2-dihydropapaverine was converted into N. methyl pavine.

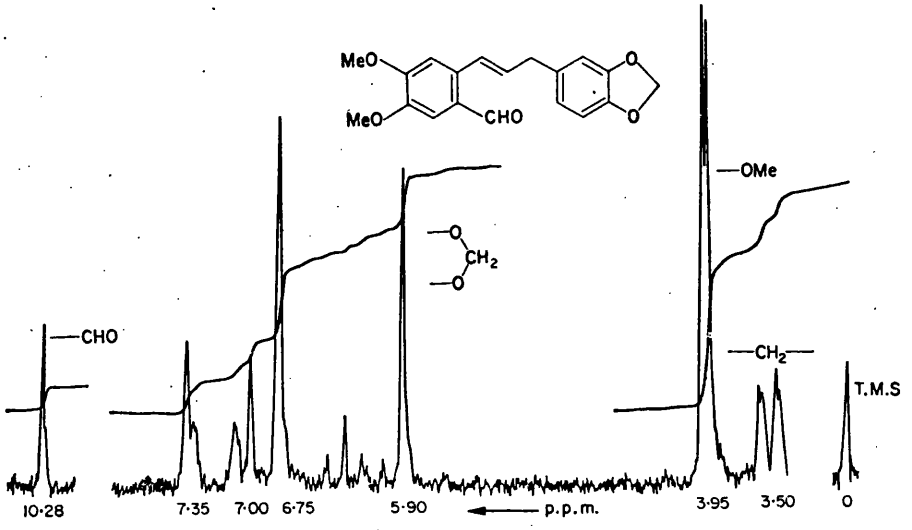


FIG. 1

EXPERIMENTAL

1-(3,4-Methylenedioxy)benzyl-6,7-dimethoxyisoquinoline. A solution of 1-(3,4-methylenedioxy) benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline[28] (14 g) in diphenyl ether (12 ml) was heated with Pd–black (1·5 g) at 170° for 4 hr, in a stream of CO_2. After cooling, the mixture was diluted with xylene (50 ml), filtered to remove the catalyst, and the filtrate extracted with 50% HCl (5 × 20 ml). The combined acid extracts were neutralized with 5% NaOH aq and extracted with benzene (3 × 20 ml). The benzene solution was washed with 2 N Na_2CO_3 aq, and then with water, dried and evaporated. The residue was crystallized from benzene–petrol (b.p. 60–80°) to yield the required isoquinoline (8·3 g) m.p. 123° (lit.,[23] m.p. 123°).

The methoidide was obtained as pale yellow prisms from EtOH m.p. 230–234°.

2-Methyl-3-(3,4-methylenedioxy) benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium salts XVII. The above methiodide (2·0 g) was added to a slurry of LAH (1·0 g) in tetrahydrofuran (150 ml) and the mixture was shaken at room temp. for 18 hr. The excess of LAH was decomposed by the cautious addition of 30% aqueous sodium potassium tartrate. The tetrahydrofuran was decanted, diluted with water and evaporated under N_2. The residual aqueous suspension was extracted with ether (3 × 50 ml) and the combined extracts dried and evaporated to leave XIV as a brown oil (1·0 g). UV absorption (qualitative in EtOH) λ_{max} 216, 294, 335 mμ; λ_{min} 275, 307 mμ. The crude base was spotted

[28] Z. Kitasato and H. Shishido, *Liebigs Ann.* **527**, 176 (1937).

onto a 0·2 mm film of silica gel and developed with a mixture of methanol:acetone:diethylamine (10:10:1) when two spots were observed R_f 0·87 and 0·69. Authentic XVII has, under the same conditions, R_f 0·69.

The crude 1,2-dihydroisoquinoline (1·0 g) was dissolved in 2% HCl (30 ml) and the solution was warmed on the water-bath for 30 min; the initial intense violet-red colour quickly faded to yellow. The solution was neutralized with $NaHCO_3$ aq or 2 N. NaOH, and extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were dried and evaporated under N_2 to leave a brown oil (0·8 g), which exhibited a green fluorescence (qualitative UV absorption in EtOH, λ_{max} 214, 245, 290 and 335 mμ; λ_{min} 228, 272 and 302 mμ). ν_{max} (liquid film) 1650 cm^{-1}.

The pseudocyanide was obtained as colourless prisms from ether m.p. 129° λ_{max}(log ε) 214(4·08), 245(3·88), 290(3·74) 315(3·56) and 350(3·72) mμ. (Found: C, 69·1; H, 6·4. $C_{21}H_{22}N_2O_4$ requires: C, 68·8; H, 6·05%.)

2-*Methyl*-3-(3,4-*methylenedioxy*)*benzyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* XIX. The 3,4-dihydroisoquinolinium hydroxide obtained above (100 mg) was dissolved in EtOH (25 ml) and water (10 ml); $NaBH_4$ (200 mg) was then added portionwise and the green fluorescence of the solution was immediately discharged. The mixture was left overnight at room temp and then evaporated to small bulk. Water (10 ml) was added and the solution extracted with ether (3 × 10 ml). The ethereal extracts were washed with water, dried and evaporated to leave a brown glass, which crystallized from EtOH to give colourless prisms (60 mg) m.p. 170–171. (Found: C, 70·4; H, 6·6; $C_{20}H_{23}NO_4$ requires: C, 70·4; H, 6·8%.)

The methiodide monohydrate was obtained from aqueous ethanol as pale brown plates m.p. 160–163° dec. (Found: C, 50·4; H, 5·8. $C_{21}H_{26}INO_4.H_2O$ requires: C, 50·3; H, 5·6%.)

1-(3,4-*Methylenedioxy*)*benzyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* XVII. This was obtained from XVI, (R = Me) by reduction with $NaBH_4$ as detailed above. Crystallization from EtOH gave colourless prisms, m.p. 116° (lit.,[28] m.p. 116°). (Found: C, 70·3; H, 6·6. Calc. for $C_{20}H_{23}NO_4$: C, 70·4; H, 6·8%.)

The methiodide monohydrate crystallized from aqueous EtOH as almost colourless small prisms, m.p. 220–223°. (Found: C, 50·4; H, 5·5. $C_{21}H_{26}INO_4H_2O$ requires: C, 50·3; H, 5·6%.)

Hofmann degradation of XIX. The methiodide of XIX (2·0 g) was heated under reflux with 35% NaOH aq (250 ml) for 36 hr. After cooling, the emulsion formed was extracted with ether (4 × 20 ml) the combined ethereal solutions were washed with water, dried and evaporated to leave the methine base (XX) as a pale yellow oil (1·1 g). The perchlorate crystallized from EtOH–ether as colourless needles m.p. 155–158° dec, λ_{max}(log ε) 271 (4·20), 292 (3·85) mμ. (Found: C, 55·4; H, 6·05. $C_{21}H_{25}NO_4.HClO_4$ requires: C, 55·3; H, 5·75%.)

A solution of the methine base (0·5 g) in $CHCl_3$ (25 ml) was treated with a stream of ozonized O_2, at room temp until the theoretical amount of O_3 had been absorbed. The solvent was removed under red. press. and the ozonide decomposed with Zn dust (0·1 g) in water (50 ml) containing one drop of 2 N $AgNO_3$. The filtered solution was extracted with ether, the ethereal solution washed with dil. HCl, then with water, dried and evaporated to leave piperonal (0·17 g) identified by mixed m.p. determination of it and its *p*-nitrophenylhydrazone with authentic specimens.

1-*Cyano*-1-(3,4-*methylenedioxy*)*benzyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. Compound XVI (R = Me; 0·2 g) was dissolved in water (6 ml) and a conc. KCN aq added. The precipitated pseudocyanide was collected and crystallized from ether, m.p. 134–135°, λ_{max}(log ε) 213 (4·29), 237 (4·14), 287 (3·97) mμ. (Found: C, 68·6; H, 6·0; $C_{21}H_{22}N_2O_4$ requires: C, 68·8; H, 6·05%.)

A mixed m.p. of this material and the pseudocyanide of the rearrangement product (XVIII) showed a clear depression. Thin film chromatograms were run on silica gel using methanol:acetone:diethylamine 10:10:1; the spots were viewed in UV light. The pseudocyanide of XVI (R = Me) had R_f 0·55 and the pseudocyanide of (XVIII) had R_f 0·78.

Degradation of (XVIII) *to the o-formylstyrene* (XXV). The pseudocyanide of (XVIII) (0·2 g) was decomposed with 5% HCl aq (5·0 ml) and the yellow solution obtained was made alkaline with 2 N NaOH in an atmosphere of N_2. Dimethyl sulphate (2·0 ml) was then added, followed by an excess of 2 N NaOH (10 ml). The mixture was heated on a water-bath for 2 hr, then cooled and extracted with ether. The combined ether extracts were washed with dil. HCl aq, dried and evaporated under N_2 to yield a pale yellow oil (0·15 g). Thin film chromatograms were conducted on silica gel using benzene:acetic acid:methanol 45:4:8 as developing solvent. Two spots at R_f 0·75 (dark green) and 0·95 (violet) were apparent on spraying with conc. H_2SO_4. Repeated recrystallization of the crude

product from MeOH eventually afforded the styrene (XXV) as yellow needles m.p. 115°, λ_{max}(log ε) 212 (4·12), 254 (4·14), 292 (3·95) mμ ν_{max} 1675 cm^{-1}. (Found: C, 70·0; H, 5·5. $C_{19}H_{16}O_5$ requires: C, 69·9; H, 5·6%.)

The oxime was crystallized from MeOH, m.p. 170°. (Found: C, 66·7; H, 5·6 $C_{19}H_{19}NO_5$ requires: C, 66·85; H, 5·6%.)

Ozonolysis of the styrene (XXV). The above styrene (XXV; 100 mg) in $CHCl_3$ (25 ml) was treated with ozonized-O_2 until no more O_3 was absorbed. The $CHCl_3$ was evaporated under red. press. and the residual gum dissolved in EtOH (2·0 ml). KOH (150 mg), water (2·0 ml), and a solution of $AgNO_3$ (200 mg) in water (2·0 ml) were added. The black suspension was swirled and warmed at 75° for 3 min, then cooled and kept overnight. The filtrate, after removal of the suspended solids, was clarified with charcoal, acidified with 50% HNO_3 aq, and extracted with ether. The extracts were worked up in the usual way to give a brown acidic gum (25 mg). This material was streaked onto a film of silica gel (1 mm thick) and the plate was developed with a 25% solution of petrol (b.p. 60–80°) in ethyl acetate. The band at R_f 0·68–0·72 was removed and extracted with boiling $CHCl_3$. The solvent was evaporated and the residue was crystallized from water to yield *m*-hemipinic acid m.p. and mixed m.p. 179–179·5°.

1,2-DIHYDROISOQUINOLINES - ACYLATION I

(Tetrahedron, 1966, 22, 2445)

Tetrahedron 1966, Vol. 22 pp. 2445 to 2452. Pergamon Press Ltd Printed in Northern Ireland

1,2-DIHYDROISOQUINOLINES—IV[1]

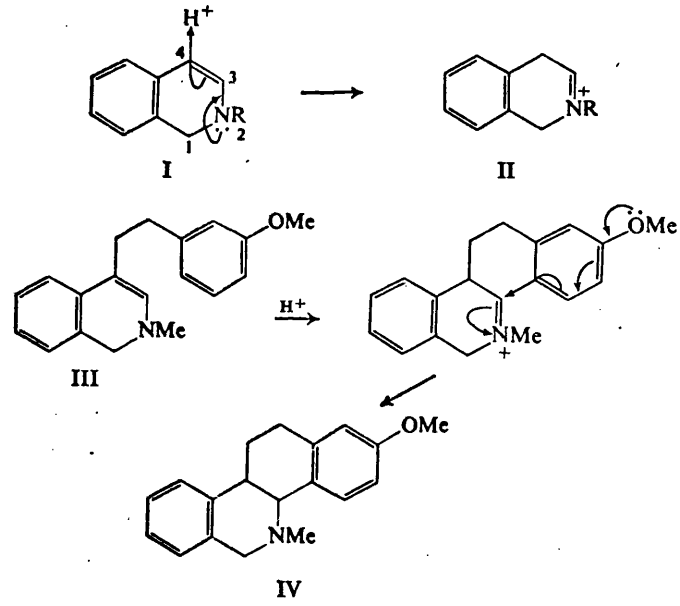
ACYLATION

M. SAINSBURY, S. F. DYKE and A. R. MARSHALL

(*Received* 9 *February* 1966)

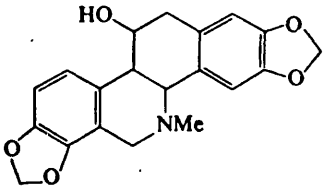
Abstract—By reacting 2-methyl-1,2-dihydroisoquinoline with acid chlorides the C_4-acylated 1,2-dihydroisoquinoline, and the corresponding 4-acylisocarbostyril are formed. Some properties of representative members of each class of product are described.

WHEN a 1,2-dihydroisoquinoline (I) is treated with mineral acid, the C_4-protonated form (II) is susceptible to nucleophilic attack at C_3, and examples of such reactions are provided by the formation of pavine from 1,2-dihydropapaverine,[2] the rearrangement of 1-benzyl-1,2-dihydroisoquinolines to the 3-benzyl-3,4-dihydroisoquinoline derivatives[3,4] and the formation of the berberine skeleton from the N-β-arylethyl-1,2-dihydroisoquinolines.[5–7] It occurred to us that a synthesis of the benzo[c]phenanthridine ring system (IV) may be achieved from a suitable 1,2-dihydro-

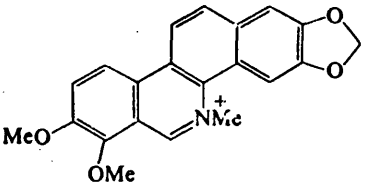


[1] Part III. D. W. Brown and S. F. Dyke, *Tetrahedron* **22**, 2437 (1966).
[2] A. R. Battersby and R. Binks, *J. Chem. Soc.* 2888 (1955).
[3] J. Knabe and J. Kubitz, *Angew. Chem.* (Int. Ed.) **2**, 689 (1963); *Arch. Pharm.* **297**, 129 (1964); J. Knabe and N. Ruppenthal, *Ibid.* **297**, 141, 268 (1964); *Naturwiss.* 482 (1964).
[4] S. F. Dyke and M. Sainsbury, *Tetrahedron Letters* 1545 (1964); *Tetrahedron* **21**, 1907 (1965).
[5] J. W. Huffman and E. G. Miller, *J. Org. Chem.* **25**, 90 (1960).
[6] A. R. Battersby, D. J. Le Count, S. Garratt and R. I. Thrift, *Tetrahedron* **14**, 46 (1961).
[7] D. W. Brown and S. F. Dyke, *Tetrahedron Letters* 3587 (1964); 1,2-Dihydroisoquinolines Part II, *Tetrahedron* **22**, 2429 (1966).

isoquinoline of the type III. The benzo[c]phenanthridine ring system is found in a few alkaloids,[8] the two main types being exemplified by chelidonine (V) and chelerythrine (VI). Syntheses of some of the fully aromatic members have been reported,[9] but the position of the hydroxyl group in alkaloids such as V, although in little doubt, has not been confirmed. Very little other synthetic work in the



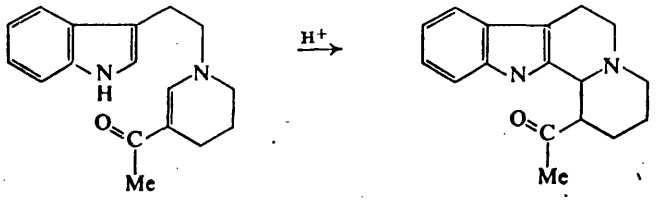
V



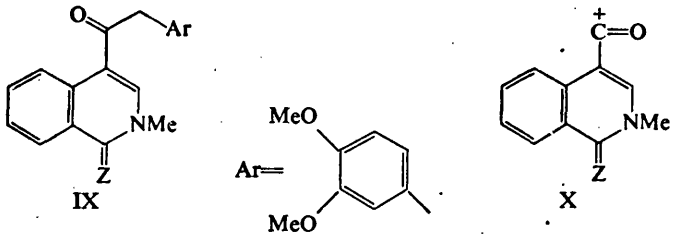
VI

benzo[c]phenanthridine series has been successful; some aspects have been briefly reviewed[10] and some other attempts described.[10] Our interest in this group of alkaloids was aroused by their possible biological activity, and we hoped to devise a more flexible synthesis than any of these previously reported. Although we have so far been unable to achieve a new synthesis of the benzo[c]phenanthridine skeleton, we wish to report here the preparation and some chemistry of potential intermediates.

4-Alkylisoquinoline derivatives can be prepared by the ring-closure of β-alkyl-β-aryl-ethylamines, but we decided to take advantage of the known enamine character of 1,2-dihydroisoquinoiines, and to prepare the model compound (IX, Z = H_2) by the interaction of 2-methyl-1,2-dihydroisoquinoline and 3,4-dimethoxyphenylacetyl chloride. We were encouraged by the report[11] that the vinylogous amide (VII) was readily ring-closed by molar hydrochloric acid solution to VIII. Since the commencement of this work, Grewe *et al.*[12] reported that 4-β-phenylethyl-1,2,3,4-



VII VIII



IX X

[8] R. H. F. M. Manske and H. L. Holmes, *The Alkaloids* Vol. IV; Chap. 35, Academic Press, New York (1954); R. H. F. Manske, *The Alkaloids* Vol. VII, p. 430, Academic Press, New York (1960).

[9] A. S. Bailey and C. R. Worthing, *J. Chem. Soc.* 4535 (1956) and Refs therein; H. R. Arthur and Y. L. Ng, *Ibid.* 4010 (1959); K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy and N. Viswanathan, *Ibid.* 4012 (1959).

[10] R. A. Abramovitch and G. Tertzakian, *Canad. J. Chem.* **41**, 2265 (1963).

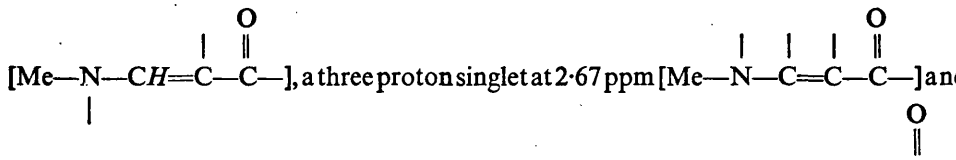
[11] E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.* **87**, 1580 (1965).

[12] R. Grewe, W. Kruger and E. Vangermain, *Chem. Ber.*, **97**, 119 (1964).

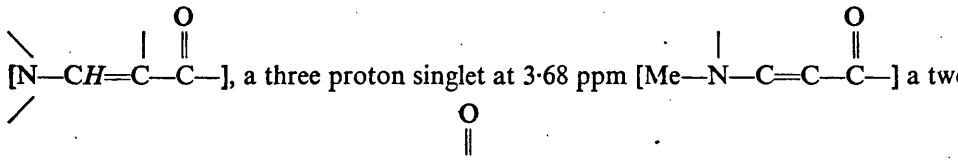
tetrahydroisoquinoline is formed by the reductive alkylation of isoquinoline with phenylacetaldehyde, but this reaction was subsequently shown[1] to yield the corresponding N-β-phenylethyltetrahydroisoquinoline instead. Bobbitt *et al.*[13] have described the preparation of 4-benzylisoquinolines by the interaction, in acid solution, of benzaldehyde and various 1,2-dihydroisoquinolines.

When equivalent amounts of 2-methyl-1,2-dihydroisoquinoline and 3,4-dimethoxyphenylacetyl chloride were allowed to react, in a nitrogen atmosphere, in benzene solution containing one equivalent of triethylamine, three neutral, nitrogenous products were isolated. The first compound, m.p. 116–118° was shown, as indicated below, to be the expected vinylogous amide (IX, Z = H_2); the second product, m.p. 167–168° was the related isocarbostyril (IX, Z = O) and the third proved to be 2-methylisocarbostyril. When a benzene solution of IX (Z = H_2) is exposed to air, or when it is treated in acetone with active manganese dioxide, the isocarbostyril (IX, Z = O) is formed. The latter compound could conceivably arise, in the acylation reaction, by acylation of some preformed 2-methylisocarbostyril, but this was shown not to be the case.

The base-peak in the mass spectrum[14] of IX (Z = H_2) occurs at *m/e* 172, corresponding to the fragment X (Z = H_2), which arises by the expected loss of the 3,4-dimethoxybenzyl group. Similarly, the base-peak in the mass spectrum of IX (Z = O) occurs at *m/e* 186, corresponding to the ion X (Z = O). The IR spectrum of IX (Z = H_2) in chloroform exhibits peaks at 1625 cm^{-1} and 1580 cm^{-1} [>C=C< and >C=O groups], whereas the IR spectrum of IX (Z = O) shows a band at 1645 cm^{-1}, characteristic of the carbonyl group in an isocarbostyril. IR carbonyl frequencies as low as 1563 cm^{-1} have been reported[15] for some enamino ketones. The NMR spectrum[16] of IX (Z = H_2) in $CDCl_3$ shows a one proton singlet at 7·5 ppm



two proton singlets at 4·45 ppm and 3·88 ppm [Ar—CH_2—N<] and [Ar—CH_2—C—]. The NMR spectrum of IX (Z = O) exhibited a one proton singlet at 8·13 ppm



proton singlet at 4·15 ppm [Ar—CH_2—C—] and a one proton multiplet at 9·02 ppm [characteristic of the C_8-H in an isocarbostyril]. The NMR spectra of vinylogous amides have been discussed in the literature.[17]

[13] J. M. Bobbitt, D. P. Winter and J. M. Kiely, *J. Org. Chem.* 30, 2459 (1965).

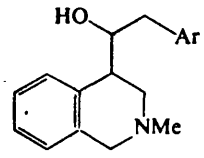
[14] Recorded on the A. E. I. MS9 Mass Spectrometer at the University of Sheffield. We are indebted to Dr. C. P. Falshaw for the measurement and discussion of the mass spectra of IX (Z = H_2) and (Z = O).

[15] G. O. Dudek, *J. Org. Chem.* 30, 548 (1965).

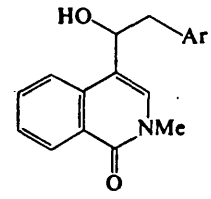
[16] NMR spectra were measured with a Varian A.60 spectrometer. Chemical shifts positions are measured in ppm downfield from TMS used as an internal standard.

[17] D. L. Ostercamp, *J. Org. Chem.* 30, 1169 (1965).

Reduction of either IX (Z = H_2 or Z = O) with LAH gave the same saturated alcohol (XI), characterized as its O-acetyl methiodide. Other examples are known[18] of the reduction of enamino ketones to saturated alcohols by this reagent. The same alcohol (XI) was produced by reducing IX (Z = H_2) with sodium borohydride. When, however, IX (Z = O) was treated with this reagent, the allylic alcohol (XII) was formed. The hydroxyl group of IX is remarkably unreactive; no oxidation



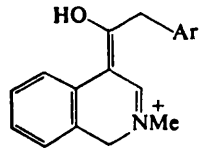
XI



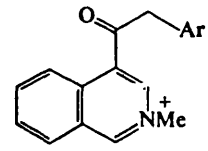
XII

occurred when it was treated with aluminium t-butoxide and benzophenone, and no apparent reaction occurred with HBr or thionyl chloride. The acetate, benzoate and tosylate were all oils.

When the vinylogous amide (IX, Z = H_2) was treated, at room temperature, with an ethanolic solution of perchloric acid a white crystalline salt was formed, from which the parent amide was released upon basification. The spectral characteristics of this perchlorate are entirely in accord with protonation of IX (Z = H_2) occurring at oxygen to yield XIII, in agreement with the behaviour of other vinylogous amides.[19] When XIII was warmed with a little perchloric acid a yellow solid was



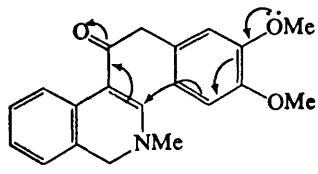
XIII



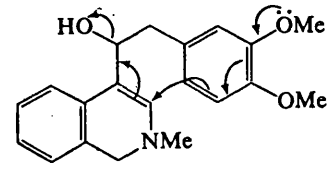
XIV

formed, from which the parent amide could not be recovered. The NMR spectrum of this yellow perchlorate (in CF_3CO_2H) was diagnostic for the fully aromatic structure XIV. Reduction of this material with sodium borohydride gave the saturated alcohol (XI); no evidence of a ring-closure could be found.

Various other attempts to ring-close IX (Z = H_2) all failed, probably because of the interaction of the nitrogen lone pair competing with the required intramolecular nucleophilic attack at C_3 (see XV). It was thought that the unsaturated alcohol (XVI)



XV

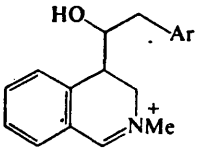


XVI

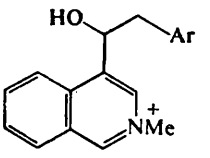
[18] See for example, Ref. 11, but see also the discussion in H. Reishagen, *Angew. Chem.* (Int. Ed). **4**, 710 (1965).

[19] G. H. Alt and A. J. Speziale, *J. Org. Chem.* **30**, 1407 (1965).

might provide a better substrate for the ring-closure. When the acetate of the saturated alcohol (XI) was dehydrogenated with iodine, two products were characterized. viz the 3,4-dihydroisoquinoline XVII and the fully aromatic structure (XVIII). Reduction of the latter with LAH followed by treatment of the intermediate 1,2-dihydroiso-



XVII



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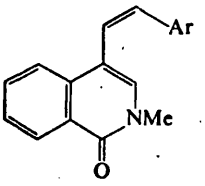


XIX

quinoline with concentrated hydrochloric acid caused disproportionation to XI and XVIII. An attempt was made to ring-close the allylic alcohol (XII), in which the nitrogen lone pair electrons are not so available, but treatment with hydrochloric acid under mild conditions gave the dehydrated product (XIX).

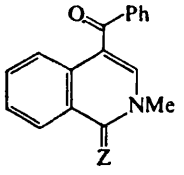
Since the acylation of a 1,2-dihydroisoquinoline constitutes a new method of preparation of 4-substituted isoquinolines, the scope of the reaction has been tested with a few other acid chlorides. The reaction between N-methyl-1,2-dihydroisoquinoline and acetyl chloride or crotonyl chloride gave complex mixtures from which it was not possible to isolate any pure material. With cinnamoyl chloride insufficient material could be isolated for study, although the NMR spectrum did

TABLE 1. THE ACYLATED ISOCARBOSTYRILS

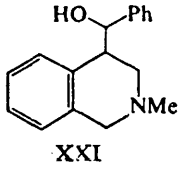
R	Molecular formula	m.p.°m from ethanol	Yield* g	λ_{max}	ε_{max}	ν_{max} cm^{-1}	Analysis Found C	H	N	Required C	H	N
Benzoyl	$C_{17}H_{13}NO_2$	134–5	1·2	226 296 307 320	21,340 11,190 11,650 8,421	1668, 1640 1625, 1605	77·8	5·2	5·2	77·55	5·0	5·3
3,4-Dimethoxy benzoyl	$C_{19}H_{17}NO_4$	179–80	0·92	222 283 324 340	31,420 15,560 18,110 13,210	1660, 1640, 1630, 1605	70·5	5·2	4·3	70·6	5·3	4·3
Phenylacetyl	$C_{18}H_{15}NO_2$	208–10	1·25	233 285 305 317	29,510 29,210 25,300 16,260	1663, 1655 1625, 1605	77·8	5·6	5·1	78·0	5·45	5·05
3,4-Dimethoxyphenylacetyl	$C_{20}H_{19}NO_4$	167–8	—	298 323 335	16,800 14,300 10,100	1655, 1645 1620	71·05	5·7	4·2	71·2	5·7	4·15

* From 10 g isoquinoline methiodide.

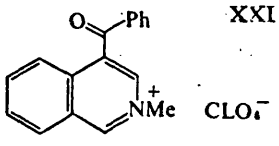
suggest that acylation had occurred as expected. Phenylacetyl, 3,4-dimethoxybenzoyl and benzoyl chlorides each reacted to give a C_4-acylated product, which was usually the isocarbostyril formed by oxidation during work up. The results are summarized in Table 1. In the case of benzoyl chloride fair yields of the vinylogous amide were obtained when N-methyl-1,2-dihydroisoquinoline was generated by the disproportionation of isoquinoline methiodide with alkali. Both XX (Z = H_2 and Z = O) were reduced to the saturated alcohol (XXI) with LAH. In this product too, the hydroxyl group was most unreactive. All attempts to convert (XX) or (XXI) to a



XX



XXI



XXII

derivative of the known[20] 4-benzylisoquinoline failed. The structures are, however, secure from the diagnostic NMR spectrum of the perchlorate (XXII) of XX (Z = H_2).

EXPERIMENTAL

M.ps are uncorrected. IR spectra were taken as nujol mulls unless otherwise stated and uv spectra were measured in EtOH solution.

2-Methyl-1,2-dihydroisoquinoline (I; R = Me). Dry, finely powdered isoquinoline methiodide (10 g) was added in small portions to a suspension of LAH (5 g) in anhydrous ether (500 ml) and the mixture was stirred for 12 hr. Excess LAH was decomposed with 30% aqueous potassium sodium tartrate under a protective atmosphere of N_2. The ethereal solution of I(R = Me) was decanted quickly and dried (Na_2SO_4) with the exclusion of atmospheric O_2.

4-[3,4-Dimethoxyphenylacetyl]2-methyl-1,2-dihydroisoquinoline (IX, Z = H_2). To the above ethereal solution of I(R = Me) was added Et_3N (1 mole equiv) and then 3,4-dimethoxyphenylacetyl chloride (1 mole equiv) in dry benzene (100 ml) was added dropwise whilst a current of N_2 was passed through the apparatus. A gelatinous precipitate was immediately formed; the mixture was heated under reflux for 5 hours and water (50 ml) was then added to dissolve the solid matter. The organic layer was separated, washed with 2N HCl (2 × 25 ml), then with water (2 × 25 ml), dried ($MgSO_4$) and evaporated under reduced press to yield a brown gum. Trituration with EtOH gave IX(Z = H_2) (1·6 g). After recrystallization from EtOH this had m.p. 116–118°. λ_{max} mμ (ε_{max}) 230 (25,120), 287 (23,990) 345 (18,200). ν_{max} cm^{-1} ($CHCl_3$) 1625, 1605, 1580. (Found: C, 73·9; H, 6·6; N, 4·5. $C_{20}H_{21}NO_3$ requires: C, 74·3; H, 6·55; N, 4·3%.)

Chromatography of the mother liquors over silica gel, and elution with chloroform petrol (60–80°) mixtures gave ethyl homoveratrate (2·4 g), 2-methylisocarbostyril (0·84 g) and 4-[3,4-*dimethoxyphenylacetyl*]2-*methylisocarbostyril* (IX, Z = O) (0·5 g). See Table 1. The acetylated isocarbostryil (56 mg) was also produced when a solution of the vinylogous amide (100 mg) in acetone (25 ml) was shaken, at room temp, with MnO_2 (100 mg) for 5 hr.

Other acylations of 2-methyl-1,2-dihydroisoquinoline. These were carried out with benzoyl, 3,4-dimethoxybenzoyl and phenylacetyl chlorides as described above. In all cases only the acetylated isocarbostryil was isolated. The results are summarized in Table 1.

4-Benzoyl-2-methyl-1,2-dihydroisoquinoline (XX, Z = H_2). Isoquinoline methiodide (10 g) was dissolved in air-free water (100 ml), and a solution of NaOH (20 g) in water (30 ml) was added with

[20] J. Braun, O. Bayer and L. Cassel, *Ber. Dtsch. Chem. Ges.* **60**, 2602 (1927).

stirring. After 30 min the brown oil that had formed was extracted into ether (total 100 ml) and this organic liquid was dried (Na_2SO_4). Triethylamine (3 ml) and benzoyl chloride (2·1 ml) were added and the mixture was heated under reflux, with stirring for 5 hr. After the addition of water (50 ml), separation of the layers, drying and evaporation of the ether solution a brown gum remained which, on trituration with benzene afforded yellow plates of XX(Z = H_2). Recrystallization from benzene gave pale yellow plates, m.p. 67–69° (1·5 g). λ_{max} mμ(ε_{max}) 288 (12,870) 295 (13,160) 323 (12,440). ν_{max} 1635, 1565. (Found: C, 84·2; H, 6·5; N, 4·5. $C_{17}H_{15}NO{\cdot}C_6H_6$ requires: C, 84·4; 6·5; N, 4·3%.)

When this compound was exposed to air, or chromatographed, or oxidized with active MnO_2, the acylated XX (Z = O) was produced.

4-[1-*Hydroxy*-2,3-(4-*dimethoxyphenyl*)*ethyl*]2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (XI). Sodium borohydride (50 mg) was added portionwise to a solution of IX (Z, = H_2) (100 mg) in EtOH (20 ml). The mixture was heated under reflux for 2 hr, the solvent was removed under reduced press and water (20 ml) was added. Extraction with ether (3 × 15 ml) followed by evaporation to dryness left a colourless meringue which could not be obtained crystalline. TLC on silica gel, with $CHCl_3$ containing 2% Et_2NH as solvent, revealed two spots (R_f 0·87 and 0·83), thought to be due to the two enantiomorphs of (XI). The methiodide of XI was obtained from EtOH–Et_2O, m.p. 80–92°. (Found: C, 53·85; H, 6·05; N, 2·8. $C_{21}H_{28}INO_3$ requires: C, 53·7; H, 6·0; N, 3·0%.)

Acetylation of XI gave an oil, the methiodide of which crystallized from EtOH as colourless needles, m.p. 224–226°. (Found: C, 54·3; H, 5·7; H, 2·5. $C_{23}H_{30}INO_4$ requires: C, 54·0; H, 5·9; N, 2·7%.)

The same saturated alcohol was obtained by reduction of IX (Z = H_2 or Z = O) with LAH under the usual conditions.

Dehydrogenation of 4-[1-*acetoxy*-2-(3,4-*dimethoxyphenyl*)*ethyl*]2-*methyl*-1,2,3,4-*tetrahydroisoquinoline*. The O-acetyl derivative of (XI) (700 mg) in EtOH (20 ml) containing anhydrous AcONa (1·5 g) was heated on a waterbath whilst a solution of I_2 (2 g) in EtOH (20 ml) was added slowly. After 3 hr heating, the straw-coloured solution was evaporated to low bulk and water (10 ml) added. SO_2 was bubbled through the solution until the I_2 colour was discharged. On standing yellow crystals of XVIII were deposited (150 gm). Recrystallization from EtOH gave m.p. 175–176°. λ_{max} mμ(ε_{max}) 235 (24,500), 280 (7,000) ν_{max} cm^{-1} 3400, 1640, 1620. (Found: C, 53·0; H, 5·1; N, 3·0. $C_{20}H_{22}INO_3$ requires: C, 53·2; H, 4·9; N, 3·1%.)

The original mother liquors were extracted with $CHCl_3$ which was then evaporated to leave a brown resin, partially soluble in hot water. KCN was added to the aqueous solution when the pseudocyanide of 4-[1-*hydroxy*-2(3,4-*dimethoxyphenyl*)*ethyl*]2-*methyl*-3,4-*dihydroisoquinoline* (XI) separated. Recrystallization from benzene–petrol (b.p. 60–80° 1:1) gave colourless needles m.p. 114–115°. (Found: C, 71·55; H, 6·7; N, 7·7. $C_{21}H_{24}N_2O_3$ requires: C, 71·6; H, 6·9; N, 8·0%.) The corresponding 3,4-dihydroisoquinolinium iodide crystallized as yellow needles from EtOH m.p. 184–186°. λ_{max} mμ(ε_{max}) 220 (32,050), 286 (15,000) ν_{max} 1670 cm^{-1}. (Found: C, 53·25; H, 5·1; N, 3·0. $C_{20}H_{24}INO_3$ requires: C, 53·0; H, 5·3; N, 3·1%.)

4-[3,4-*Dimethoxyphenylacetyl*]2-*methylisoquinolinium perchlorate* (XIV); The amide IX (Z = H_2; 0·5 g) in EtOH (10 ml) was treated with 60% aqueous perchloric acid (1 ml). After standing overnight, colourless crystals had separated (0·42 g). Recrystallization from EtOH gave XIII as colourless prisms, m.p. 178–180°. λ_{max} mμ(ε_{max}) 237 (34,670) 280, (12,300), 240 (11,750); ν_{max} cm^{-1} 3300, 1662, 1610. (Found: C, 56·3; H, 5·5; N, 3·2. $C_{20}H_{21}NO_3{\cdot}HClO_4$ requires: C, 56·7; H, 5·2; N, 3·3%.)

When a quantity of this perchlorate was warmed in EtOH containing a little perchloric acid, yellow needles of XIV were deposited (82% conversion). Recrystallization from $CHCl_3$ gave yellow needles, m.p. 188–189°. λ_{max} mμ(ε_{max}) 232 (26,300), 281 (13,700), 333 (12,250); ν_{max} cm^{-1} 17,00 1645, 1615. (Found: C, 56·7; H, 5·0; N, 3·6. $C_{20}H_{20}NO_3{\cdot}HClO_4$ requires: C, 56·9; H, 4·8; N, 3·3%.)

4-*Benzoyl*-2-*methylisoquinolinium perchlorate* (XXII). The amide XX (Z = H_2; 100 mg) in EtOH (10 ml) was warmed with 60% aqueous perchloric acid (1 ml). When cooled, a crystalline deposit (85 mg) of XXII formed. Recrystallization from EtOH gave yellow needles, m.p. 216–218°; λ_{max} mμ(ε_{max}) 221 (41,320), 323 (6,071); ν_{max} cm^{-1} 1665, 1645, 1635. (Found: C, 58·7; H, 4·3; N, 3·7. $C_{17}H_{14}NO{\cdot}HClO_4$ requires: C, 58·7; H, 4·1; N, 4·0%.)

4-[1-*Hydroxy*-2-(3,4-*dimethoxyphenyl*)*ethyl*]2-*methylisocarbostyril* (XII). Sodium borohydride

(150 mg) was added in small portions to a suspension of IX (Z = O; 150 mg) in MeOH (20 ml). After heating the mixture under reflux for 2 hr, the solvent was removed and water (20 ml) added. Extraction with benzene (3 × 15 ml) afforded a gum which, upon trituration with ether, gave colourless prisms (120 mg). Recrystallization from EtOH gave colourless prisms of XII, m.p. 150–151°; λ_{max} mμ(ε_{max}) 230 (25,900), 285 (9,770), 330 (4,250); ν_{max} cm^{-1} 3375, 1650, 1625. (Found: C, 70·7; H, 6·3; N, 4·0. $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 4·1%.)

Treatment of XX (Z = O) with $NaBH_4$ in MeOH at room temp yielded a product corresponding to XII m.p. 171–172° as small white needles. (Found: C, 76·5; H, 5·2; N, 5·6; $C_{17}H_{15}NO_3$ requires: C, 77·0; H, 5·7; N, 5·13%.) Reduction of either XX (Z = H_2) or (Z = O) with LAH under standard conditions gave XXI. The methiodide was obtained from EtOH as small prisms m.p. 123–125°. (Found: C, 55·4; H, 6·2; N, 3·4; I, 32·55. $C_{18}H_{22}INO$ requires: C, 54·9; H, 5·8; N, 3·5; I, 32·1%.)

4-[3,4-*Dimethoxystyril*]2-*methylisocarbostyril* (XIX). A solution of XII (50 mg) in benzene was saturated with HCl during 15 min. Removal of the solvent under reduced press gave a crystalline residue, recrystallization of which from AcOEt yielded XIX (36 mg) as stout colourless prisms, m.p. 132–134°; λ_{max} mμ(ε_{max}) 278 (16,000), 333 (21,750); ν_{max} cm^{-1} 1640, 1635, 1615. (Found: C, 74·7; H, 6·1; N, 4·8; OMe, 19·2. $C_{18}H_{13}NO(OMe)_2$ requires; C, 74·7; H, 6·0; N, 4·40 OMe, 19·35%.)

THE CONDENSATION OF ISOQUINOLINIUM SALTS WITH AROMATIC ALDEHYDES

(Tetrahedron Letters, 1966, 3755)

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Printed in Great Britain.

THE CONDENSATION OF ISOQUINOLINIUM SALTS WITH AROMATIC ALDEHYDES

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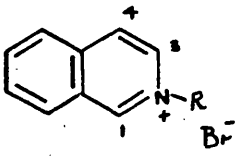
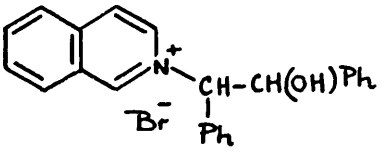
(Received 2 June 1966)

In 1935 Krohnke[1] reported that benzaldehyde condensed with 2-benzyl-isoquinolinium bromide (1, R = $CH_2C_6H_5$), in the presence of alkali, to yield, after acidification with HBr, an alcohol, formulated as (2). Since it is probable that the pseudobase (3, R = $CH_2C_6H_5$) is formed from (1) and the alkali, it seemed to us that a more likely structure for Krohnke's compound is (5, R = $CH_2C_6H_5$), formed as indicated in (3) ⟶ (4) ⟶ (5), the pseudobase behaving as an enamine.



(1)



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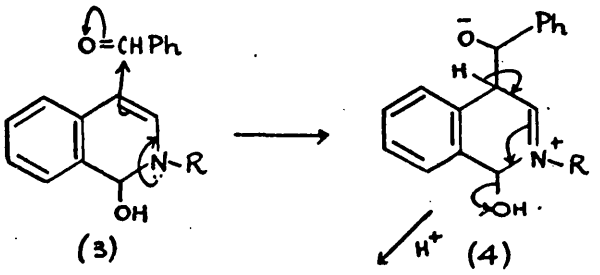
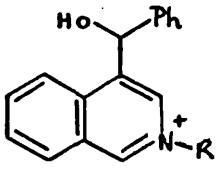
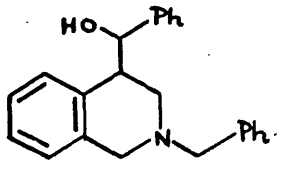


(3) (4)



(5)

Krohnke's original directions were repeated and a quaternary bromide, m.p. 218° was isolated as described. The N.M.R. spectrum[2] of this compound (measured in trifluoracetic acid with TMS as an internal reference) was found to be diagnostic for structure (5). In particular one proton singlets at 9.7 ppm and 8.9 ppm are characteristic for the C_1 and C_3 hydrogens respectively of an isoquinolinium ion. Since the C_3—hydrogen appears as a singlet, the C_4 position must be substituted; the benzylic methylene group absorbs as a sharp singlet at 6.0 ppm (and at 6.4 ppm in (1, R = $CH_2C_6H_5$) itself). Reduction of Krohnke's compound with sodium borohydride gave the alcohol[3] (6), m.p. 116°. We had previously shown[4] that the interaction of 2-methyl-1,2-dihydroisoquinoline (7, R = CH_3) with aromatic acid chlorides yield the 4-acyl derivatives (8, R = CH_3), and that reduction of these products with lithium aluminium hydride give the saturated alcohols (9). The interaction of 2-benzyl-1,2-dihydroisoquinoline (7, R = $CH_2C_6H_5$) and benzoyl chloride gave (8, R = $CH_2C_6H_5$; Ar = C_6H_5) and this, on reduction with LAH resulted in material identical with (6).



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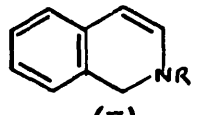

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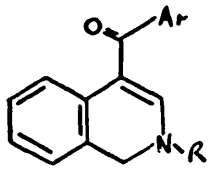

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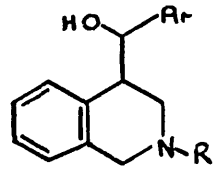

(9)

In view of our interest in 1,2-dihydroisoquinoline chemistry and C_4-substituted isoquinoline derivatives, we are examining the scope of this reaction in more detail.

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3. Satisfactory analyses were obtained for all compounds reported.
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SYNTHESIS OF MUNETONE

(J.Chem.Soc.C., 1966, 749)

Synthesis of Isoflavones. Part IV.[1] Munetone

By S. F. Dyke, W. D. Ollis, and M. Sainsbury

Synthesis has established that the structure (I) originally suggested for munetone is not correct. A revised structure (XXII) for munetone is confirmed by its partial synthesis from mundulone (II).

THE isoflavone munetone was first isolated by N. L. Dutta[2] from the root bark of the Indian variety of *Mundulea sericea* (Willd.) Chevalier (*Mundulea suberosa* Benth.) and it was given the constitution (I).[3] Our interest in these studies[2] was stimulated by our investigation[4] of the extractives of the root bark of African *Mundulea sericea*, which had already led to the isolation of a number of interesting new natural products including mundulone[5] (II), sericetin[4,6] (III), leaserone[4,7] (IV), munduserone[8] (V), and sermundone[4,7] (VI). As munetone was not among the natural products which we first isolated from this plant source, we decided to investigate the structure (I) suggested for munetone by synthesis. Meanwhile in a later study of a different source of *Mundulea sericea*, we also isolated munetone.[7]

The structure (I) assigned[2,3] to munetone was unusual in two respects. Munetone was described as lacking an oxygen-containing substituent in the 4′-position, yet this is frequently encountered among the natural isoflavones.[9,10] As far as we are aware, the only other known isoflavone which is not oxygenated in the 4′-position is tlatlancuayin[11] (VII). The structure (I) also contains a C_5-isoprenoid residue which is unique in structural type among the variations[12] associated with natural phenolic compounds, but its existence in structure (I) was apparently placed beyond doubt by the claim to have obtained isotubaic acid (IX) and 2-methoxybenzoic acid by the alkaline oxidative degradation of munetone.[3] However, these conclusions were invalidated by the following synthetic studies.[13]

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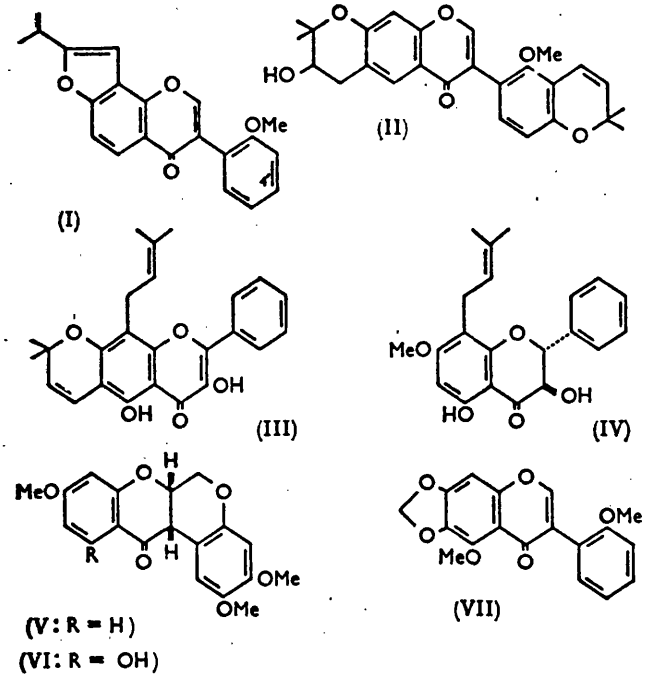
[12] W. D. Ollis and I. O. Sutherland, "Recent Development in the Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon, Oxford, 1961, p. 74.
[13] For a preliminary report see S. F. Dyke, W. D. Ollis, and M. Sainsbury, *Proc. Chem. Soc.*, 1963, 179.

Our first synthetic objective was the deoxybenzoin (VIII), but the Hoesch reaction [14] between isotubanol (X)



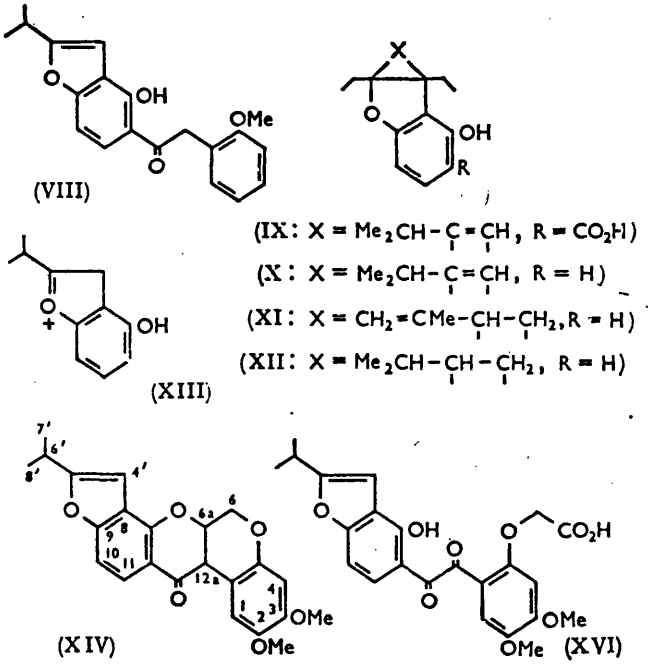
(I) (II) (III) (IV) (V: R = H) (VI: R = OH) (VII)

and 2-methoxybenzyl cyanide, the boron trifluoride-catalysed *C*-acylation [15] of isotubanol (X) by 2-methoxyphenylacetic acid, and the Friedel–Crafts reaction [16] between isotubanol (X) and 2-methoxyphenylacetyl chloride, failed. In connection with these syntheses, isotubanol (X) has been prepared previously by the alkaline hydrolysis of isorotenone [17] (XIV) to isotubaic acid [18] (IX) followed by thermal decarboxylation.[18] Although 6a,12a-dehydrorotenone is described [19] as yielding only derric acid on treatment with alkali and hydrogen peroxide, we find that 6a,12a-dehydroisorotenone [20] (XV) does yield isotubaic acid by reaction with alkaline hydrogen peroxide. The course of this degradation is not established, but the route probably involves the benzil [21] (XVI) as an intermediate which has also been isolated with isotubaic acid (IX) as another oxidation product of 6a,12a-dehydroisorotenone.

The failures in the attempted transformation of isotubanol (X) into the deoxybenzoin (VIII) were attributed to deactivation of isotubanol towards electrophilic attack as a result of either protonation to give the conjugate acid (XIII), or the corresponding reaction with a Lewis acid. An alternative route [22] to deoxybenzoins was therefore examined which involved the attempted reaction of *O*-acetylisotubaic acid chloride and ethyl 2-methoxyphenylacetate. This reaction also failed. An attempted Hoesch reaction between tubanol (XI) and 2-methoxybenzyl cyanide was not successful.

These failures in the tubanol and isotubanol series encouraged an examination of reactions with dihydrotubanol (XII). The Fries rearrangement of the ester (XVII) was unsuccessful and although a satisfactory reaction did take place between dihydrotubanol (XII) and 2-methoxyphenylacetic acid in the presence of boron trifluoride,[15,23] the product was not the required deoxybenzoin (XVIII). Its ultraviolet and infrared spectra and the absence of a coloration with ferric chloride showed that the product was in fact the isomeric ketone (XIX).

The synthesis of the isoflavone (I) was eventually completed by the following series of reactions. The Hoesch reaction of dihydrotubanol [24] (XII) with 2-methoxybenzyl cyanide gave the ketone (XVIII) which, by reaction with ethyl orthoformate,[25] gave the isoflavone



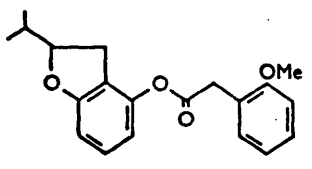
(VIII) (IX: X = $Me_2CH-C=CH$, R = CO_2H) (X: X = $Me_2CH-C=CH$, R = H) (XI: X = $CH_2=CMe-CH-CH_2$, R = H) (XII: X = $Me_2CH-CH-CH_2$, R = H) (XIII) (XIV) (XVI)

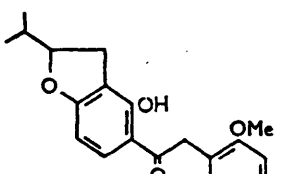
(XV) Double bond at C(6a) – C(12a)

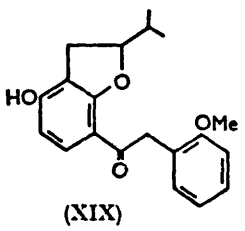
(XX). This isoflavone (XX) was dehydrogenated either with *N*-bromosuccinimide [26] followed by heating with pyridine, or directly by heating with palladised charcoal.

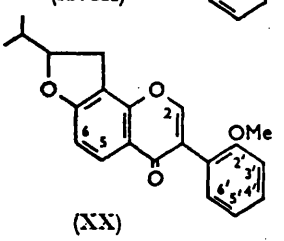
[14] P. E. Spoerri and A. S. Du Bois, *Org. Reactions*, 1949, **5**, 387.
[15] Cf. S. S. Karmacker, K. H. Shah, and K. Venkataraman, *Proc. Indian Acad. Sci.*, 1953, **37***A* 660.
[16] Cf. W. B. Whalley, *J. Chem. Soc.*, 1953, 3366.
[17] A. Butenandt and F. Hildebrandt, *Annalen*, 1929, **477**, 245.
[18] S. Takei, *Ber.*, 1929, **61**, 1003.
[19] F. B. La Forge and L. E. Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1091.
[20] L. Crombie, P. J. Godin, D. A. Whiting, and K. S. Siddalingaiah, *J. Chem. Soc.*, 1961, 2876.
[21] F. B. La Forge and H. L. Haller, *J. Amer. Chem. Soc.*, 1932, **54**, 810.
[22] Cf. L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1951, **34***A*, 187.
[23] K. Kinder, H. Oelschlager, and P. Henrich, *Arch. Pharm.*, 1954, **287**, 210; P. de Re and L. Cimatoribus, *J. Org. Chem.*, 1961, **26**, 3650.
[24] M. Miyano and M. Matsui, *Bull. Agric. Chem. Soc. Japan*, 1959, **23**, 141; *Chem. Ber.*, 1959, **92**, 2487.
[25] V. R. Sathe and K. Venkataraman, *Current Sci. (India)*, 1949, **18**, 373.
[26] P. S. Sarin, J. M. Sehgal, and T. R. Seshadri, *J. Sci. Ind. Res. (India)*, 1957, **16***B*, 61.

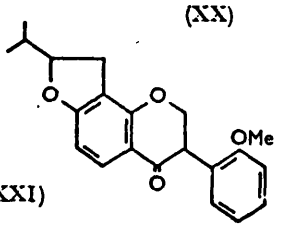
The dehydrogenation product was certainly the isoflavone (I), and this was confirmed by its catalytic hydrogenation to give a tetrahydro-derivative which was the


(XVII)


(XVIII)

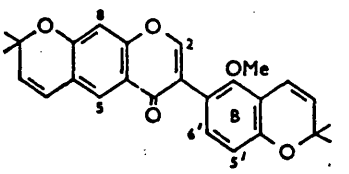

(XIX)

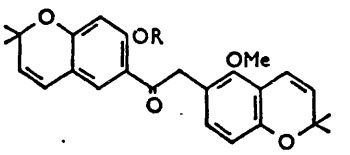

(XX)


(XXI)

isoflavanone (XXI). However, comparison of the synthetic isoflavone (I) with natural munetone kindly supplied by Dr. N. L. Dutta established that they were not identical.

The nuclear magnetic resonance spectrum of natural munetone was then determined.[27] This spectrum was clearly incompatible with the constitution (I) and the proton count indicated that the molecuar formula should be changed from $C_{21}H_{18}O_4$ to $C_{26}H_{24}O_5$. The suspicion that munetone was an anhydro-derivative of mundulone (II) was immediately reinforced by a detailed examination of the nuclear magnetic resonance spectrum of munetone which exhibited signals highly characteristic of *two* 2,2-dimethylchromene[6] systems. Thus the spectrum showed two singlets, τ 8·53 and 8·50, each corresponding to six protons and two AB systems to be associated with four protons. The high-field doublets of each AB system could be seen at τ 4·25 and 4·34 (J = 10 c./sec.), but the two low-field doublets (τ ~3·5) were not clearly discernible owing to overlapping. The rest of the spectrum was easily analysed. It showed a singlet (τ 6·38) due to one methoxyl group and a singlet (τ 1·94) due to the proton in position 2 of the isoflavone skeleton.[28] Of four aromatic protons, two were to be associated with two singlets (τ 1·97 and 3·17) which were slightly coupled (J = 0·6 c./sec.) indicating a pair of *para*-related protons, and two with an AB system (τ 3·33 and 2·72; J = 8 c./sec.) due to a pair of *ortho*-related protons. The singlet (τ 1·97) was characteristically deshielded and was therefore associated with a proton in position 5;[28] its weak coupling suggested a second proton (τ 3·17) was in position 8. The *ortho*-pair of protons were therefore located on ring B in positions 5′ and 6′ and their chemical shifts (τ 3·33 and 2·72) and biogenetic analogy favoured the structure (XXII) as the most reasonable structure for munetone.


(XXII)


(XXIII: R = H)
(XXIV : R = Me)

This structural suggestion (XXII) for munetone was established by its partial synthesis from mundulone[5] (II). Mundulone methanesulphonate and ethanolic sodium hydroxide gave a deoxybenzoin (XXIII) identical with munetol,[2] which by reaction with ethyl orthoformate gave munetone (XXII). Independent studies by Professor Venkataraman and his colleagues[29] of the mass spectrum and nuclear magnetic resonance spectrum of munetone have led to the same conclusion regarding its constitution.

EXPERIMENTAL

Isorotenone (XIV).—Concentrated sulphuric acid (350 ml.) was slowly added to a stirred solution of rotenone (200 g.) in glacial acetic acid (1225 ml.) and the mixture was warmed for 10 min., cooled, and poured into water (4 l.). The precipitate was collected, washed, and crystallised from aqueous acetone giving the product (130 g.; 65%) as colourless needles, m. p. 180°. Further recrystallisation gave isorotenone, m. p. 184° (lit.,[17] m. p. 176°). Its n.m.r. spectrum ($CDCl_3$ solution) showed signals characteristic of (*a*) the Me_2CH–C=CH grouping: τ 8·72, doublet, J = 7 c./sec., Me_2CH–; τ 7·02, septet, J = 7 c./sec., Me_2CH–; τ 3·60, singlet, >C=CH–; and (*b*) the rotenoid residue: τ 6·26, singlet, $(OMe)_2$; τ 4·9—6·3, multiplet, –CH–CH–CH_2–O; τ 3·54, singlet, 4-H; τ 3·26, singlet, 1-H; AB system (τ 2·23 and τ 3·00; J = 9 c./sec.), 11-H and 10-H (see XIV).

6a,12a-*Dehydroisorotenone* (XV).—Iodine (100 g.) in ethanol (1 l.) was added during 5 hr. to a solution of isorotenone (100 g.) and fused potassium acetate (500 g.) in boiling ethanol (2·5 l.). The total volume was reduced to about one-third by distillation under diminished pressure and the mixture kept at 0° overnight. The yellow crystalline precipitate was collected. The filtrate was acidified with ethanolic sulphuric acid (10%), the precipitated potassium sulphate removed and washed with ethanol. The filtrate and washings were concentrated to yield a further

[27] See spectrum No. 696, N.M.R. Spectra Catalogue, Varian Associates, 1963.

[28] J. Massicot and J.-P. Marthe, *Bull. Soc. chim. France*, 1962, 1962; J. S. P. Schwarz, A. I. Cohen, W. D. Ollis, E. A. Kaczka, and L. M. Jackman, *Tetrahedron*, 1964, 20, 1317.

[29] C. S. Barnes, J. L. Occolowitz, N. L. Dutta, P. Madhavan Nair, P. S. Phadke, and K. Venkataraman, *Tetrahedron Letters*, 1963, No. 5, 281.

quantity of yellow crystalline precipitate. The combined product was washed well with water and recrystallised from a mixture of ethanol (350 ml.) and chloroform (175 ml.) giving 6*a*,12*a*-dehydroisorotenone (79 g.; 79%) as yellow prisms, m. p. 198° (lit.,[20] m. p. 195—196°).

Oxidation of 6a,12a-Dehydroisorotenone with Hydrogen Peroxide in Alkaline Solution.—Small portions of hydrogen peroxide (100 vol., 225 ml.) and aqueous potassium hydroxide (25 g. in 150 ml.) were added alternately during 4 hr. to a boiling solution of 6a,12a-dehydroisorotenone (25 g.) in methanol (4 l.). The methanol was then removed under diminished pressure, water (250 ml.) added, and the mixture extracted with ether (3 × 100 ml.). The alkaline layer was acidified with 2N-sulphuric acid, extracted with benzene, and the combined benzene extracts shaken with saturated aqueous sodium hydrogen carbonate (4 × 30 ml.). The hydrogen carbonate extracts were acidified and shaken with benzene; removal of the benzene gave a residue (3·52 g.) which was chromatographed on silica gel.

Elution with 50% benzene–light petroleum (b. p. 60—80°) gave a fraction (1·92 g.) which was crystallised from aqueous ethanol giving a product (1·47 g., 10%) as a white powder, m. p. 183—184°. Recrystallisation from dilute acetic acid gave isotubaic acid (IX) as large, colourless prisms, m. p. 187° (lit.,[30] m. p. 182°), $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH 233 mμ (51,300), 309 mμ (3460). The n.m.r. spectrum of isotubaic acid (IX) ($CDCl_3$ solution) shows a doublet, τ 8·67; J = 7 c./sec., $Me_2\underset{|}{C}H-$; a septet, τ 6·95, J = 7 c./sec., $Me_2\underset{|}{C}H$; a singlet, τ 3·47, slightly broadened ($J \sim 1$ c./sec.) by long-range coupling, benzofuran H; an AB system, τ 3·06 and 2·30; J = 9 c/sec.; the high-field signal shows a long range coupling ($J \sim 1$ c./sec.), two *ortho*-aromatic H; broad band, τ 0·92, the hydroxyl H and carboxyl H.

Further elution with benzene gave a yellow crystalline solid (1·2 g.) which was recrystallised from ethanol giving the benzil (XVI) as yellow prisms, m. p. 186° (lit.,[21] m. p. 195°); $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 242 mμ (33,240), 283 mμ (14,510), 343 mμ (7250); $\nu_{max.}$ in $CHCl_3$ 3290, 1775, 1660, 1635, and 1615 cm.$^{-1}$.

Ethyl 2-Methoxyphenylacetate.—A mixture of 2-methoxyphenylacetic acid (6·0 g.), obtained by alkaline hydrolysis of 2-methoxybenzyl cyanide,[31] concentrated sulphuric acid (1 ml.) and ethanol (50 ml.) was heated under reflux for 7 hr. Excess of ethanol was removed under diminished pressure, water added, and the ester isolated by chloroform extraction. Distillation gave *ethyl 2-methoxyphenylacetate* (5·61 g.; 78%) as a colourless oil, b. p. 158°/18 mm. (Found: C, 68·23; H, 7·18. $C_{11}H_{14}O_3$ requires C, 68·04; H, 7·22%).

2-Isopropyl-4-(2′-methoxyphenylacetyloxy)-2,3-dihydrobenzofuran (XVII).—2-Methoxyphenylacetic acid (5 g.) and thionyl chloride (12 ml.) were heated under reflux for 1 hr. Distillation under diminished pressure gave 2′-methoxyphenylacetyl chloride (4·9 g.; 81%), b. p. 96—98°/1 mm.

2-Methoxyphenylacetyl chloride (3 ml.) was added during 30 min. to a stirred solution of dihydrotubanol[24] (XII) (2·74 g.) in pyridine (10 ml.) at 0°. After standing overnight at room temperature, the solution was poured on crushed ice and dilute hydrochloric acid. Extraction with chloroform followed by chromatography on silica gel gave, by elution with light petroleum (b. p. 60—80°)–benzene (80 : 20 v/v), a fraction (0·77 g.) which was recrystallised from light petroleum (b. p. 40—60°) giving the *ester* (XVII) as colourless plates, m. p. 66—67° (Found: C, 73·50; H, 6·81. $C_{22}H_{22}O_4$ requires C, 73·60; H, 6·79%).

4-Hydroxy-2-isopropyl-7-(2′-methoxyphenylacetyl)-2,3-dihydrobenzofuran (XIX).—A solution of dihydrotubanol (XII) (1 g.) and 2-methoxy phenylacetic acid (1·5 g.) in xylene (8 ml.) was saturated at 0° with boron trifluoride–hydrogen fluoride (liberated from potassium fluoroborate by the addition of concentrated sulphuric acid[23]). After warming at 70° for 5 min., the mixture was poured on ice and extracted with chloroform. This extract yielded a solid which was recrystallised from hot light petroleum (b. p. 100—120°) giving *4-hydroxy-2-isopropyl-7-(2′-methoxyphenylacetyl)-2,3-dihydrobenzofuran* (0·45 g.) as colourless prisms, m. p. 143° (Found: C, 73·46; H, 6·45. $C_{20}H_{22}O_4$ requires C, 73·60; H, 6·79%); $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 222 mμ (20,890), 282 mμ (16,600); $\nu_{max.}$ in $CHCl_3$, 3080 and 1690 cm.$^{-1}$. It gave no obvious coloration with ethanolic ferric chloride.

4-Hydroxy-2-isopropyl-5-(2′-methoxyphenylacetyl)-2,3-dihydrobenzofuran (XVIII).—A mixture of dihydrotubanol (XII) (5·9 g.), 2′-methoxyphenylacetonitrile (6·0 g.), and powdered anhydrous zinc chloride (6·5 g.) in anhydrous ether (100 ml.) was cooled to 0° and saturated with hydrogen chloride during 5 hr. After storing at 0° for 3 days, the ethereal layer was decanted from the lower layer which was washed with a further quantity of ether (2 × 200 ml.). The intermediate ketimine hydrochloride was heated with water (50 ml.) on a steam-bath and the solid which separated on cooling was collected by chloroform extraction. Removal of the chloroform and recrystallisation from aqueous ethanol gave *4-hydroxy-2-isopropyl-5-(2′-methoxyphenylacetyl)-2,3-dihydrobenzofuran* (6·95 g.; 65%) as colourless prisms, m. p. 104° [Found: C, 73·46; H, 6·80; OMe, 9·80. $C_{21}H_{19}O_3$(OMe) requires C, 73·60; H, 6·79; OMe, 9·51%]; $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH 226 mμ (28,180), 285 mμ (14,130); $\nu_{max.}$ in $CHCl_3$, 3400 and 1630 cm.$^{-1}$. It gave a blood-red colour with ethanolic ferric chloride.

Treatment of this ketone with ethanolic 2,4-dinitrophenylhydrazine and concentrated sulphuric acid gave its *2,4-dinitrophenylhydrazone* as red prisms, m. p. 150—151°, from aqueous acetic acid (Found: C, 61·29; H, 5·26; N, 11·06. $C_{26}H_{26}N_4O_7$ requires C, 61·85; H, 5·17; N, 11·06%).

2′-Methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)isoflavone (XX).— 4-Hydroxy-2-isopropyl-5-(2′-methoxyphenylacetyl)-2,3-dihydrobenzofuran (0·5 g.), ethyl orthoformate (1 ml.), piperidine (10 drops), and anhydrous pyridine (10 ml.) were heated under reflux for 12 hr., cooled, and poured on crushed ice and dilute hydrochloric acid. After standing the solid was collected and crystallised from aqueous ethanol giving *2′-methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)isoflavone* (0·31 g., 64%) as colourless prisms, m. p. 155° [Found: C, 75·0; H, 6·01; OMe, 9·15. $C_{20}H_{17}O_3$(OMe) requires C, 74·98; H, 5·99; OMe, 9·22%]; $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 218 mμ (23,440), 248 mμ (33,110), 302 mμ (12,020); $\nu_{max.}$ (Nujol) 1645 and 1631 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$ solution) showed signals characteristic[32] of (*a*) the $Me_2CH-\underset{|}{C}H(O-)-CH_2$ grouping: τ 8·99, quartet, Me_2; τ ~8·0, multiplet, $\geq CH$; τ ~5·3, multiplet, $-\underset{|}{C}H-O$; τ ~6·8, multiplet, $\geq CH_2$; and (*b*) the isoflavonoid

[20] T. Reichstein and R. Hirt, *Helv. Chim. Acta*, 1933, **16**, 121.
[21] W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1953, 1860.
[32] S. Goodwin, J. N. Shoolery, and L. F. Johnson, *J. Amer. Chem. Soc.*, 1959, **81**, 3065; see spectrum No. 325, N.M.R. Spectra Catalogue, Varian Associates, 1962.

grouping: τ 2·09, singlet, 2-*H*; AB system (τ 1·89 and 3·20; J = 8·5 c./sec.), 5-*H* and 6-*H*; τ 2·5—3·3, multiplet, 3'-, 4'-, 5'-, and 6'-*H*; τ 6·28, singlet, 2'-OMe (see XX).

2'-Methoxy-7,8-(2-isopropylfurano)isoflavone (I).—(*a*) 2'-Methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)isoflavone (1 g.), *N*-bromosuccinimide (0·5 g.), and benzoyl peroxide (0·1 g.) in pure carbon tetrachloride (40 ml.) were heated under reflux for 1 hr. The precipitated succinimide was removed and evaporation of the carbon tetrachloride gave a residue. This was dissolved in pure pyridine (8 ml.), heated under reflux for 90 min., poured into dilute hydrochloric acid, and extracted with chloroform. The material from this extract was chromatographed on silica gel and elution with benzene gave a fraction (520 mg.) which by careful fractional crystallisation from ethanol eventually gave *2'-methoxy-7,8-(2-isopropylfurano)isoflavone* (22 mg.), m. p. 184° [Found: C, 74·91; H, 5·88; OMe, 9·89. $C_{20}H_{15}O_3$(OMe) requires C, 75·43; H, 5·43; OMe, 9·28%]; $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 225 mμ (21,880), 275 mμ (10,960), 310 mμ (7580); $\nu_{max.}$ (Nujol) 1640 and 1630 cm.$^{-1}$.

(*b*) 2'-Methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)isoflavone (200 mg.) and palladised charcoal (30%, 200 mg.) were heated at 290° in nitrogen for 4 hr. The mixture was continuously extracted with ethyl acetate and removal of the solvent gave a crystalline residue (50 mg.), which by fractional crystallisation from ethanol gave the isoflavone (8 mg.) identical with that obtained by method (*a*).

2'-Methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)isoflavanone (XXI).—Catalytic hydrogenation at atmospheric pressure of 2'-methoxy-7,8-(2-isopropyl-2,3-dihydrofurano)-isoflavone (100 mg.) in glacial acetic acid (3 ml.) with a palladium–charcoal catalyst (30%, 75 mg.) for 1 hr. gave the isoflavanone (XXI) (75 mg., 72%) as colourless microprisms, m. p. 127—129°, from aqueous ethanol (Found: C, 74·35; H, 6·96. $C_{21}H_{22}O_4$ requires C, 74·53; H, 6·55%); $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 220 mμ (28,840), 245 mμ (20,890), 295 mμ (11,010); $\nu_{max.}$ (Nujol) 1675, 1640, and 1630 cm.$^{-1}$.

Munetol (XXIII).—A suspension of mundulone methanesulphonate [5] (2·6 g.) and sodium hydroxide (13·7 g.) in 50% aqueous ethanol (100 ml.) was heated under reflux in nitrogen for 45 min. After cooling and acidification with dilute hydrochloric acid, extraction with ethyl acetate (3 × 50 ml.) yielded a gum. This was chromatographed on silica gel and elution with benzene–light petroleum (b. p. 60—80°) (50 : 50 v/v) followed by crystallisation from light petroleum (b. p. 60—80°) yielded munetol (0·39 g.) as pale yellow needles, m. p. 123° (lit.,[2] m. p. 128°) (Found: C, 74·08; H, 6·45. Calc. for $C_{25}H_{26}O_5$: C, 73·86; H, 6·45%); $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 227 mμ (30,200), 259 mμ (31,620), 318 mμ (5100); $\nu_{max.}$ ($CHCl_3$) 1640 and 1607 cm.$^{-1}$. It gave a dark green colour with ethanolic ferric chloride.

Munetol Methyl Ether (XXIV).—A mixture of munetol (200 mg.), dimethyl sulphate (4 ml.) and anhydrous potassium carbonate (1 g.) in acetone (10 ml.) was heated under reflux for 16 hr., then poured into water. The precipitate was collected and crystallised from aqueous ethanol giving munetol methyl ether (132 mg.) as colourless prisms, m. p. 139° (lit.,[2] m. p. 139°) [Found: C, 74·21; H, 6·70; OMe, 14·82. Calc. for $C_{24}H_{22}O_3$(OMe)$_2$: C, 74·26; H, 6·71; OMe, 14·75%].

Munetone.—A mixture of munetol (100 mg.), ethyl orthoformate 0·2 ml.), piperidine (2 drops), and pyridine (2 ml.) was heated under reflux for 8 hr., then cooled and poured into dilute hydrochloric acid. The precipitate was collected and crystallised from ethanol giving munetone (53 mg.; 52%) as colourless prisms, m. p. 192° (lit.,[2] m. p. 192—193°) [Found: C, 74·69; H, 6·03; OMe, 7·94. Calc. for $C_{25}H_{21}O_4$(OMe): C, 74·98; H, 5·81; OMe, 7·44%]; $\lambda_{max.}$ ($\varepsilon_{max.}$) in EtOH, 230 mμ (30,900), 265 mμ (38,020), 328 mμ (11,480); $\nu_{max.}$ (Nujol) 1640 and 1610 cm.$^{-1}$. This material was identical in all respects with natural munetone.[2,7]

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A SIMPLE BENZO[c]PHENANTHRIDINE RING SYNTHESIS

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1,2-DIHYDROISOQUINOLINES—V[1]
A SIMPLE BENZO[C]PHENANTHRIDINE RING SYNTHESIS

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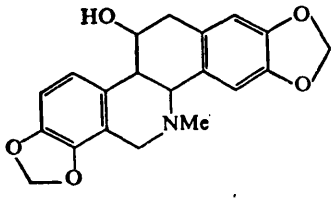
Abstract—The known[2] 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**33**) has been synthesized in a simple procedure utilizing a 1,2-dihydroisoquinoline and a photochemical ring-closure reaction.

THE benzo[c]phenanthridine ring system is found in a small group of alkaloids,[3] the two main types being exemplified by chelidonine (**1**) and chelerythrine (**2**). The majority possess the 2,3,8,9-tetra-oxygenation pattern shown, but nitidine[4] (**3**) and avicine[5] (**4**) are exceptions. Chelerythrine (**2**) was the first alkaloid of the group to be synthesized,[6] in a ten-step sequence, from opianic acid (**5**). Subsequently both nitidine[7] and avicine[8] were prepared by essentially the same route, but as yet none of the reduced members of type **1** have been synthesized. Benzo[c]phenanthridin eitself was first reported[9] by Graebe, who prepared it from chrysene, and although several



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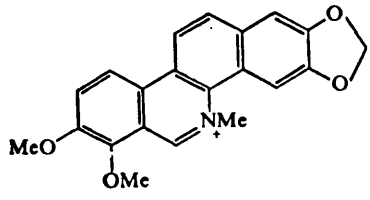

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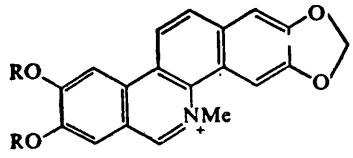
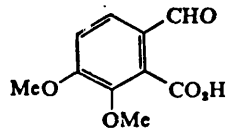


3, R = Me
4, R, R = —CH_2—



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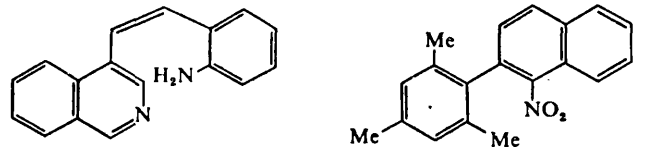
[1] Part IV. M. Sainsbury, S. F. Dyke and A. R. Marshall, *Tetrahedron* **22**, 2445 (1966).
[2] A. S. Bailey, Sir R. Robinson and R. S. Staunton, *J. Chem. Soc.* 2277 (1950).
[3] R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. IV; Chap. 35. Academic Press, New York (1954); R. H. F. Manske, *The Alkaloids* Vol. VII; p. 430, Academic Press, New York (1960).
[4] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 1840 (1959).
[5] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 4007 (1959).
[6] A. S. Bailey and C. R. Worthing, *J. Chem. Soc.* 4535 (1956).
[7] H. R. Arthur and Y. L. Ng, *J. Chem. Soc.* 4010 (1959); K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy and N. Viswanathan, *Ibid.* 4012 (1959).
[8] K. W. Gopinath, T. R. Govindachari and N. Viswanathan, *Tetrahedron* **14**, 322 (1961).
[9] C. Graebe, *Liebigs Ann.* **335**, 122 (1904); C. Graebe and F. Honigsberger, *Ibid.* **311**, 257 (1900); C. Graebe and R. Guehm, *Ibid.* **335**, 113 (1904).

methods have been described[10] for the construction of the ring system, very little systematic chemistry has been studied. Of the several attempted ring syntheses since the last review,[10] some successful ones include the Pschorr ring-closure with[11] the amine **6** and the oxidation,[12] via a nitrene intermediate, of the nitrocompound **7**. In neither case is the starting material easily accessible. The tetrahydro derivative **9** has been obtained[13] by cyclodehydration of the anil **8**, and more recently,[14] the ketones **13** (R = H or OMe) have been obtained from the α-naphthylamines **10** (R = H or OMe) as shown in **10** + **11** → **12** → **13**.

We planned to utilize the enamine character of 1,2-dihydroisoquinolines[15] as the basis of a synthesis of the alkaloids of both types **1** and **2**; our unsuccessful attempts to ring-close the model compound **14** (Z = H_2), itself prepared by the C_4-acylation



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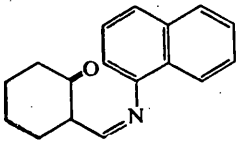

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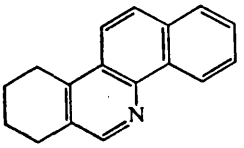

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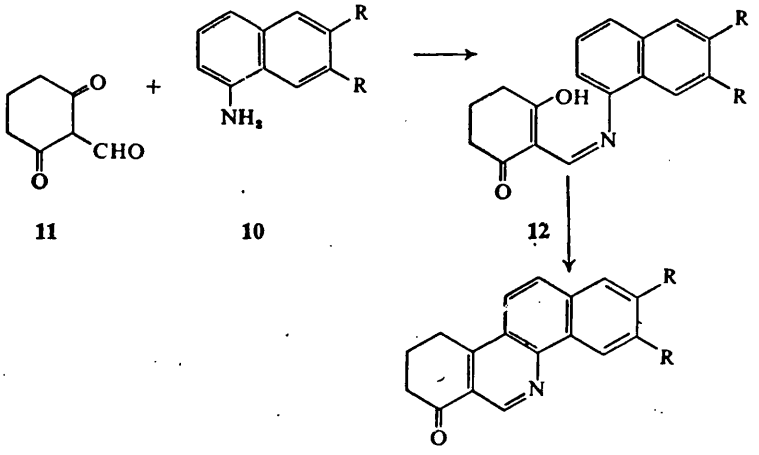


11 **10** **12**

13

[10] J. V. Crawford in *The Chemistry of Heterocyclic Compounds: Six Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings* (Edited by C. F. H. Allen) p. 157. Interscience, New York (1951).

[11] R. A. Abramovitch and G. Tertzakian, *Canad J. Chem.* **41**, 2265 (1963).

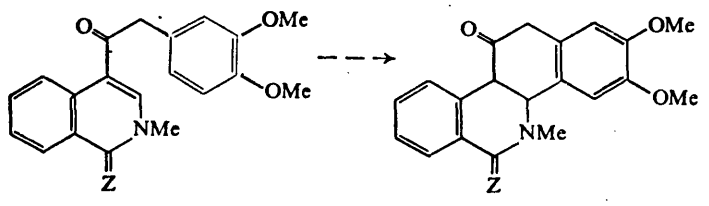
[12] R. A. Abramovitch, O. Newman and G. Tertzakian, *Canad. J. Chem.* **41**, 2390 (1963).

[13] B. L. Hollingsworth and V. Petrow, *J. Chem. Soc.* 1537 (1948).

[14] S. V. Kessar, I. Singh and A. Kumar, *Tetrahedron Letters* 2207 (1965).

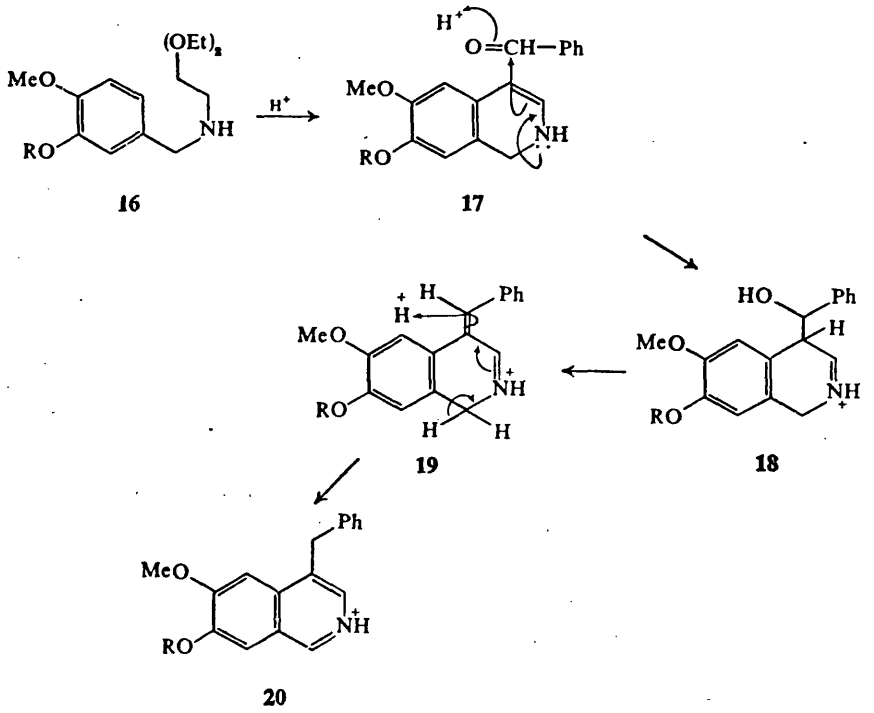
[15] S. F. Dyke and M. Sainsbury, *Tetrahedron* **21**, 1907 (1965) and Refs therein cited.

of a 1,2-dihydroisoquinoline, to the ketone **15** have already been described.[1] We now wish to report a simplified route to the fully aromatic benzo[c]phenanthridine ring system which employs a 1,2-dihydroisoquinoline intermediate, and a photochemical ring-closure reaction. The method will be illustrated for the known[2] 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**33**).



14 **15**

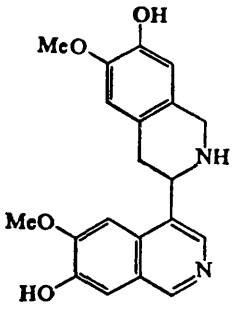
Bobbitt *et al.*[16] have found that 1,2-dihydroiosquinolines (e.g. **17**, R = H) can conveniently be formed by treating aminoacetals such as **16**, (R = H) with mineral acids, and they have shown that these intermediates give 1,2,3,4-tetrahydroisoquinolines by reduction, or 4-benzylisoquinolines by condensation with benzaldehyde, in good yields. The latter reaction proceeds, presumably, as shown in **16** → **20**. In all of the examples reported,[17] a phenolic OH group was present in the 6,7 or 8-position



16 **17** **19** **18** **20**

[16] J. M. Bobbitt, J. M. Kiely, K. L. Khanna and R. Ebermann, *J. Org. Chem.* **30**, 2247 (1965); J. M. Bobbitt, D. P. Winter and J. M. Kiely, *Ibid.* **30**, 2459 (1965).

[17] NMR spectra were measured with a Varian A.60 spectrometer. Chemical shifts are expressed in c/s or ppm downfield from TMS as an internal standard and refer to $CDCl_3$ solns unless otherwise stated. IR spectra were recorded using Nujol nulls.



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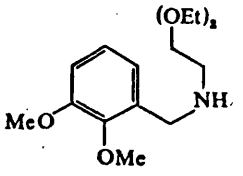

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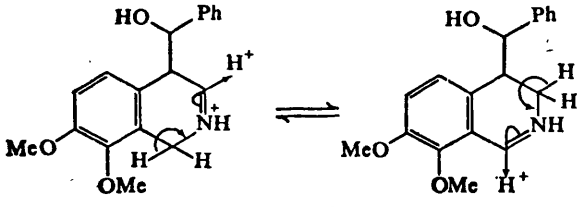
of the 1,2-dihydroisoquinolines, and the only by-products characterized were the expected dimers of the type **21**.

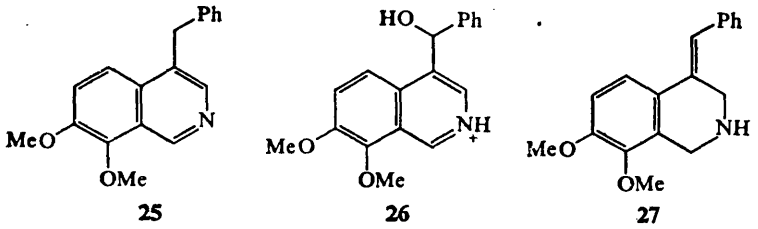
We have now extended this work to the less reactive aminoacetals **16**, (R = Me) and **22**.

With the latter and benzaldehyde a white crystalline hydrochloride quickly formed which could not be obtained analytically pure. Bands at 3400 and 1660 cm^{-1} in its IR spectrum indicated the presence of —OH and $>C{=}\overset{+}{N}H$-groups respectively; the NMR spectrum[17] (taken in CF_3CO_2H soln) is compatible with either structure **23** or **24**. Whereas **23** corresponds to the expected intermediate in the C_4-benzylation reaction,

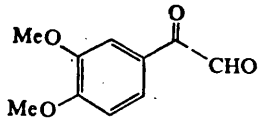


23 24

24 is in accord with the UV evidence (the spectrum suggests the presence of a 3,4-dihydroisoquinolinium salt). The two are, however, easily interconvertible, and the fully aromatic end-product is readily derivable from either. Structure **23** or **24** is supported by the fact that when heated at 70° *in vacuo*, or under reflux with ethanolic KOH, the compound is converted into 7,8-dimethoxy-4-benzylisoquinoline (**25**), a structure confirmed by the analysis, the UV spectrum and the diagnostic NMR spectrum. When the hydrochloride **23** or **24** is boiled with hydrogen chloride in ethanol in the presence of air, the isoquinolinium salt **26** is produced, whereas reduction with sodium borohydride yields **27**, presumably by way of a normal reduction of



25 26 27



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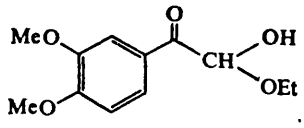

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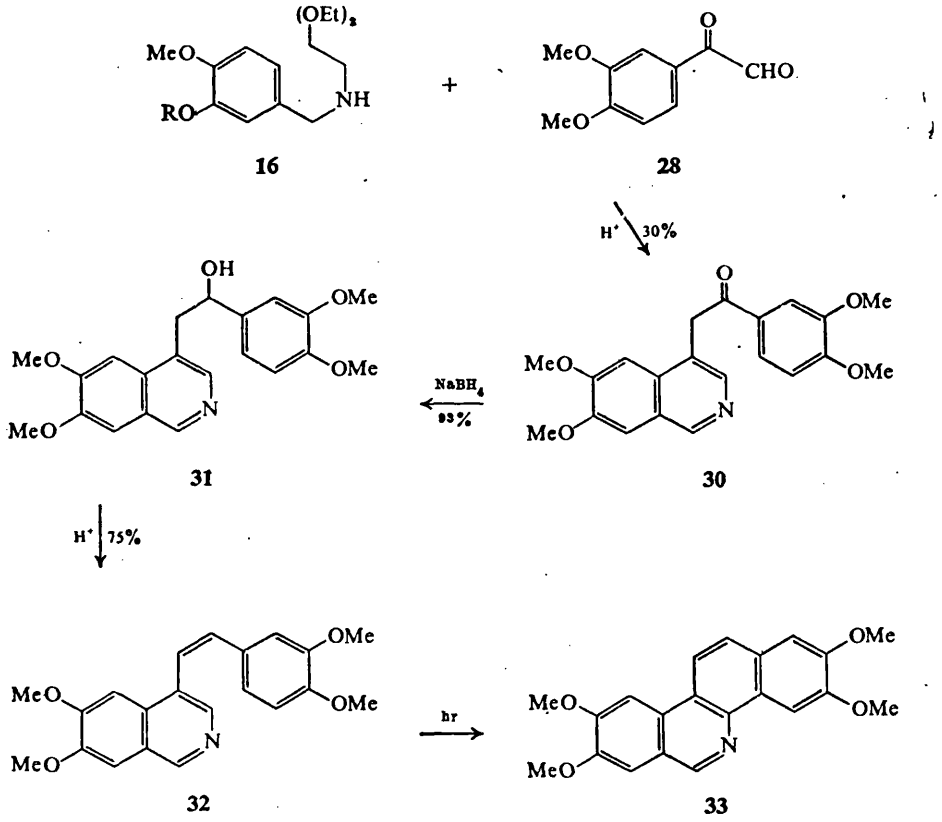
the >C=NH+-group and a base-catalysed elimination. A parallel series of experiments with the aminoacetal **16** (R = Me) and benzaldehyde, *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde was conducted. The nitroaldehyde failed to react under the conditions employed,* but in the other cases intermediates corresponding to **23** or **24** were isolated, together with the expected 4-benzylisoquinolines. The results are summarized in the Experimental.

The new synthesis of 2,3,8,9-tetramethoxybenzo[c]phenanthridine **33** is summarized in the Chart I. The 3,4-dimethoxyphenylglyoxal (**28**) was obtained in 77% yield by the oxidation of acetoveratrone with selenium dioxide. The pale yellow product, m.p. 124–126° was shown by mol. wt determination and by its NMR spectrum to be the hemiacetal **29**, which, on heating above its m.p., reverts to the glyoxal. The interaction of **28** and **16** (R = Me) led to an insoluble hydrochloride which, upon basification

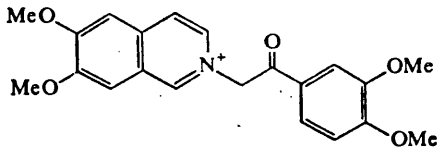
Chart I



* Various nitrobenzaldehydes have now been successfully employed; the results will be described in a later paper.

gave a solid, m.p. 179–180°. This material analysed for $C_{21}H_{21}NO_5$ and its NMR spectrum was diagnostic for the required isoquinoline structure **30**. The base was further characterised as the hydrochloride and methiodide.

The acid filtrate from **30** was evaporated to leave a sticky solid which crystallized from ethanol to give a compound which melted at 80°, with effervescence, solidified, then remelted at 156–160°. The IR spectrum of this compound, tentatively assigned the structure **35**, exhibited bands at 3300 cm^{-1} (—OH), 1675 cm^{-1} (>C=O) and 1640 cm^{-1} (>C=C<). Basification gave an unstable oil, whereas treatment with mineral acid gave a crystalline quaternary salt which possessed a CO group (1683 cm^{-1}), but no OH group. The NMR spectrum of this hydrochloride **35** in CF_3CO_2H was identical with that of the quaternary salt in the same solvent and showed amongst



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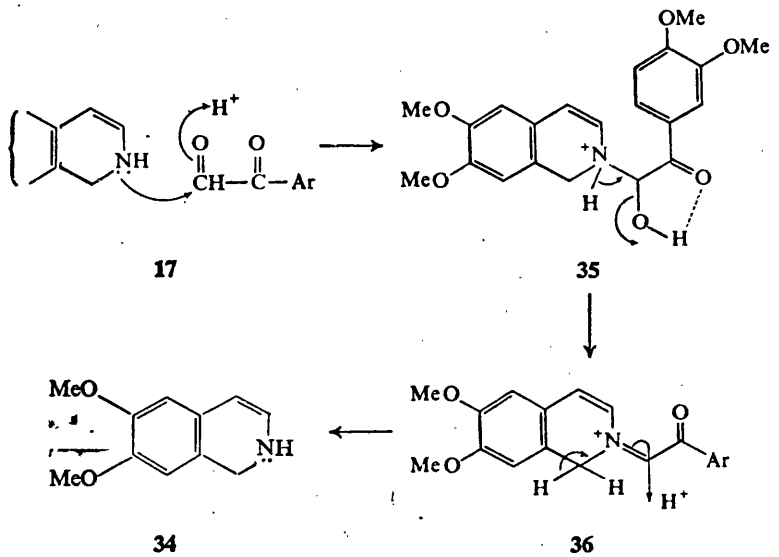
other absorptions, a one proton singlet at 9·0 ppm (C_1—H of an isoquinolinium salt), a broadened two proton singlet at 8·1 ppm (C_3 + C_4 hydrogens of an isoquinoline ring) and a two proton singlet at 6·15 ppm (—C(=O)—CH_2—N⊂). The structure **34** for the quaternary salt was confirmed by its preparation from 6,7-dimethoxyisoquinoline and ω-bromoacetoveratrone. Hence, as well as C_4-alkylation of the 1,2-dihydroisoquinoline **17**, N-alkylation can occur, at least with an arylglyoxal, to yield **35** which, upon heating, or upon treatment with acids is transformed into **34**, probably via **36**.

Reduction of the ketoisoquinoline **30** [Chart I] with sodium borohydride gave the secondary alcohol **31**, which was easily dehydrated by HCl in chloroform to the styrene



17 **35**

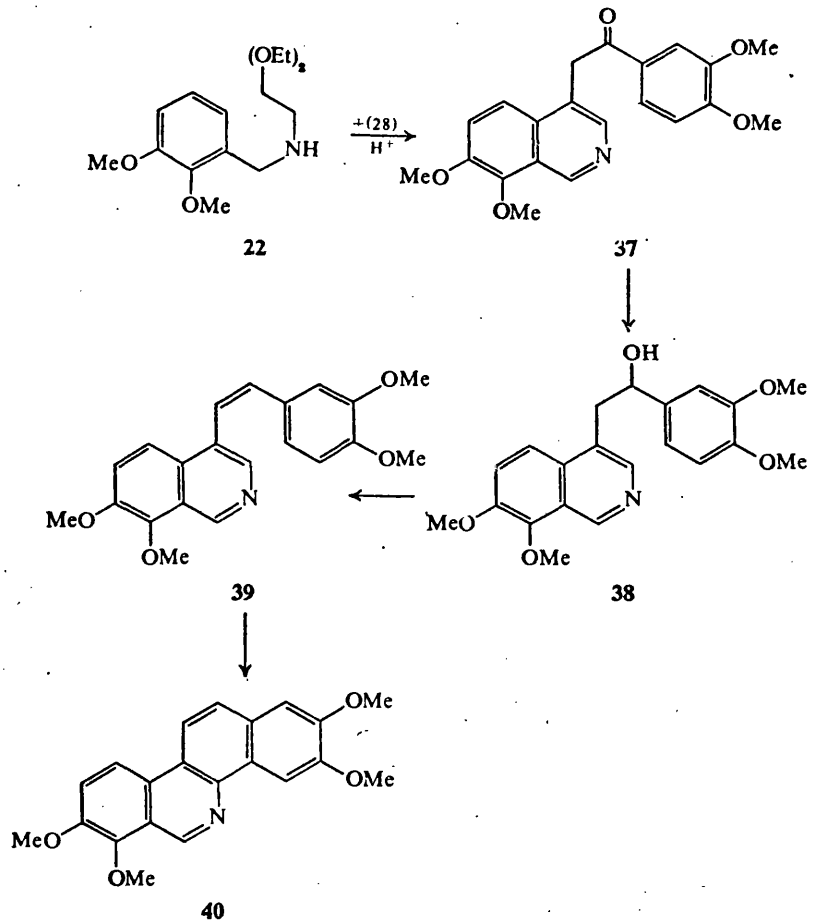
34 **36**

32, and this, when irradiated[18] in ethanol solution according to the conditions used by Timmons[19] caused the precipitation of 2,3,8,9-tetramethoxybenzo[c]phenanthridine (33). Purification was achieved by sublimation and crystallization from pyridine to give a product whose m.p. was undepressed when mixed with an authentic specimen[20] of 33.

A similar sequence of reactions [Chart II] led, from the glyoxal 28 and the isomeric aminoacetal 22, through the ketoisoquinoline 37 and the alcohol 38 to the styrene 39. The conditions for the photochemical ring-closure of 39 were far more critical since the expected product 40 is soluble in the ethanol solvent, but eventually a minute quantity of 2,3,7,8-tetramethoxybenzo[c]phenanthridine (40) was obtained.

The necessary modifications to this route that will lead to the synthesis of the natural alkaloids will be described later.

Chart II



[18] A Hanovia photochemical reactor was used.

[19] We are grateful to Dr. C. J. Timmons for experimental details of his photochemical synthesis of the parent benzo[c]phenanthridine prior to publication.

[20] It is a pleasure to thank Dr. A. S. Bailey for providing a specimen of 2,3,8,9-tetramethoxybenzo[c]-phenanthridine.

EXPERIMENTAL[17]

4-Benzyl-7,8-dimethoxyisoquinoline(25). The acetal **22**, (28·3 g) was dissolved in conc HCl(250 ml) containing EtOH (125 ml) warmed to 60°, then benzaldehyde (21·2 g) was added. After heating under reflux for 1 hr, the dark coloured soln was cooled and stored at 0° for 48 hr; the solid which had separated was then collected. Crystallization first from HCl—EtOH (1:1) and then from water gave **23** or **24** as colourless needles (11 g) m.p. 100–105°. ν_{max} cm^{-1}, 3500 (—OH), 1665 (>C=$\overset{+}{N}$<). λ_{max} (ε) mμ, 236 (13,000), 350 (8,360). NMR singlet 8·5 ppm. [1] (C_1 or C_3), singlet 5·25 ppm [2] (—CH_2—$\overset{+}{N}$<). (Found: C, 64·10; H, 5·62; N, 4·01. $C_{18}H_{19}NO_3HCl$ requires: C, 64·79; H, 6·04; H, 4·20%.)

The filtrate from the above separation was washed with benzene, evaporated to dryness and the residue recrystallized from EtOH to yield 4-benzyl-7,8-dimethoxyisoquinoline hydrochloride as pale yellow needles (10 g) m.p. 178°; ν_{max} cm^{-1}, 1630 (>$\overset{+}{N}$=C<), 1605 (>C=C<); λ_{max} (ε) mμ, 235 (13,500), 255 (8360), 280 (1650), 360 (1360). NMR singlet 8·9 ppm [1] (C_1), singlet 8·0 ppm, [1] (C_3), singlet 3·1 ppm [2] (Ar–CH_2–). (Found: C, 68·54; H, 5·41; N, 4·74; Cl, 11·80. $C_{18}H_{17}NO_2$, HCl requires: C, 68·42; H, 5·70; N, 4·43; Cl, 11·22%.) Basification of this material with aqueous ammonia eventually afforded the free base **25** as a sticky solid which could not be obtained crystalline; ν_{max} cm^{-1}, 1635 (>C=$\overset{+}{N}$<), 1608 (>C=C<); λ_{max} (ε) mμ, 236 (15,800), 270 (1480), 280 (1480), 350 (1640). NMR singlet 8·8 ppm [1] (C_1), singlet 8·3 ppm [1] (C_3), 2·83 ppm, [2] (—CH_2—Ar).

Reduction of this base with $NaBH_4$ in aqueous EtOH gave the 1,2,3,4-tetrahydro base as a colourless liquid which was characterized as the hydrochloride. Colourless needles, m.p. 187–188°, from EtOH. (Found: C, 68·00; H, 6·21. $C_{18}H_{20}NO_2$·HCl requires: C, 68·02; H, 6·35%.)

The alcohol hydrochloride **23** or **24** when heated with methanolic KOH gave 4-benzyl-7,8-dimethoxyisoquinoline which was characterized as the hydrochloride and which is identical with the material described above.

4-(α-Hydroxybenzyl)7,8-dimethoxyisoquinoline hydrochloride(26). The alcohol hydrochloride **23** or **24**, (1 g) was boiled with EtOH previously saturated with HCl and after 4 hr the solvent was removed. The residue was recrystallized from EtOH to yield **26** as pale yellow prisms (0·1 g) m.p. 165–170°; ν_{max} cm^{-1}, 3350 (—OH), 1635 (>C=$\overset{+}{N}$<), 1610 (>C=C<), λ_{max} mμ, 240, sh. 255, 350. NMR singlet 8·8 ppm [1] (C_1) singlet 8·4 ppm [1] (C_3), singlet 3·75 ppm [1] (Ar—C(OH)*H*—) (Found: C, 65·01; H, 5·21; N, 4·02. $C_{18}H_{17}NO_3$, HCl requires: C, 65·18; H, 5·47; N 4·23%.)

4-Benzylidene-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (27). The alcohol hydrochloride **23** or **24**, (5 g) in 90% aqueous EtOH (100 ml) was treated with $NaBH_4$ (5 g), and the mixture heated on a water-bath for 1 hr. After standing overnight the EtOH was removed and water (50 ml) was added. The insoluble material was collected into benzene and subsequent removal of the dried solvent gave **27** as colourless needles (3·5 g), m.p. 144–145°, from benzene; ν_{max} cm^{-1}, 1620 (>C=C<) λ_{max} (ε) mμ, 236 (14,800), 303 (18,600). (Found: C, 76·63; H, 6·73; N, 5·11. $C_{18}H_{19}NO_2$ requires: C, 76·84; H, 6·81; N, 4·98%.)

The hydrochloride was obtained as colourless prisms from EtOH, m.p. 227–228°. (Found: C, 68·16; H, 6·28; N, 4·71; Cl, 11·03. $C_{18}H_{19}NO_2$·HCl requires: C, 68·00; H, 6·34; N, 4·40; Cl, 11·15%.)

Catalytic reduction of **27** in EtOH containing a trace of perchloric acid, using Adam's catalyst, gave 4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline. This substance was characterized as the hydrochloride and was shown to be identical with the compound previously obtained by $NaBH_4$ reduction of **25**.

4-Benzyl-6,7-dimethoxyisoquinoline hydrochloride (**20**, R = Me) [with Miss M. E. Chilton]. A soln of **16** (R = Me, 10 g) in conc HCl (50 ml) containing EtOH (25 ml) was heated to boiling under an atmosphere of N_2 and benzaldehyde (10 g) was added. After heating under reflux for 45 min, the soln was cooled and washed with benzene. Evaporation under reduced press gave a sticky residue which was taken up in a small volume of EtOH and set aside. Compd (**18**, R = Me) was eventually deposited as a microcrystalline orange coloured solid (4·56 g, 34·6%), m.p. 180–185°, ν_{max} cm^{-1}, 3350 (–OH), 1660 (>C=$\overset{+}{N}$<); λ_{max} (ε) mμ, 245 (27, 530). NMR (CD_3SOCD_3), singlet 7·95 ppm [1] (C_1 or C_3), singlet 4·55 ppm [2] (—CH_2—$\overset{+}{N}$<), broad singlet 4·10 ppm [1] (—O*H*) removable by deuteration.

The ethanolic mother liquor from the above experiment was evaporated under reduced press and the residue obtained dissolved in water. After repeatedly washing with benzene the aqueous phase was concentrated to small volume and cooled to 0°, when (**20**, R = Me) was obtained as colourless needles (0·93 g), m.p. 192–194° from water; ν_{max} cm^{-1}, 1630 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} (ε) mμ 240, (16,760), 313 (10,000). NMR (CF_3CO_2H), doublet 9·15 ppm [1] J = 6·1 c/s (C_3), doublet 8·20 ppm, [1] J = 6·1 c/s. (C_3), singlet 4·52 ppm [2] (—C*H*$_2$—Ar). (Found: C, 68·35; H, 5·79; N, 4·65. $C_{18}H_{18}NClO_2$ requires: C, 68·40; H, 5·72; N, 4·44%.)

Compd (**18**, R = Me) (500 mg) was heated under reflux with 0·5N methanolic KOH (50 ml) for 1 hr. Removal of the solvent and addition of water (5 ml) followed by extraction of the aqueous phase with ether, gave, after removal of the dried ether, 4-benzyl-6,7-dimethoxyisoquinoline (335 mg) as an oil. This compound was characterized as the hydrochloride, and shown to be identical with **20** prepared previously.

4-(p-*Methoxybenzyl*)6,7-*dimethoxyisoquinoline hydrochloride.* In a similar experiment to that described above, **16** (R = Me) was reacted with *p*-methoxybenzaldehyde. The alcohol hydrochloride corresponding to **23** or **24** was obtained in 47% yield as a red crystalline solid, m.p. 155–156°; ν_{max} cm^{-1}, 3250 (—OH), 1665 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} mμ 250, 290. NMR (CD_3SOCD_3), singlet 9·5 ppm, [1] (C_1 or C_3), singlet 4·5 ppm, [1] (—O*H*) removed by deuteration. (Found: C, 66·46; H, 5·91; N, 3·43. $C_{19}H_{20}NClO_3$ required: C, 66·00; H, 5·80; N, 4·05%.)

Evaporation of the mother-liquor, from which the alcohol hydrochloride had separated, gave 4-(*p*-methoxybenzyl)6,7-dimethoxyisoquinoline, which was characterized as the hydroiodide, pale yellow prisms, m.p. 188–189° from EtOH; ν_{max} cm^{-1}, 1640 (>C=$\overset{+}{N}$<), 1620 (>C=C<); λ_{max} (ε) mμ 243 (20,050), 313 (15,850). NMR (CF_3CO_2H), doublet 9·3 ppm, [1] J = 5·4 c/s (C_1), doublet 8·1 ppm, [1] J = 5·4 c/s, (C_3), singlet 4·50 ppm, [2] (C*H*$_2$—Ar). (Found: C, 52·58; H, 4·74; N, 3·24. $C_{19}H_{20}NIO_4$ requires: 52·30, H, 4·58; N, 3·20%.)

3,4-*Dimethoxyphenylglyoxal* (**28**). Acetoveratrone (72 g) was added rapidly to a well stirred, warm soln of SeO_2 (49 g) in EtOH (240 ml) containing water (9 ml). After heating under reflux for 24 hr the precipitated Se was removed by filtration and the filtrate evaporated under reduced press. The residual liquid was distilled (135–138°/0·15 mm) to yield the monomeric glyoxal as a pale yellow liquid (60 g, 77%); ν_{max} cm^{-1}, 1679, 1660. NMR singlet 9·60 ppm (—C*H*O). On standing, the liquid solidified to a glass, which when triturated with 75% EtOHaq yielded pale yellow prisms (m.p. 124–126° from aqueous EtOH), ν_{max} cm^{-1}, ~3300 (—OH), 1665 (>CO), 1095 (—O—). Analytical results for this compound were inconsistent due to the presence of variable amounts of water, which could not be removed. Heating under vacuum resulted in reformation of the aldehydic monomer, hemiacetal m.p. 77–78° from EtOH. (Found: C, 59·70; H, 6·65; $C_{12}H_{16}O_5$ requires C, 59·99; H, 6·71%)

4-(3,4-*Dimethoxyphenacyl*) 6,7-*dimethoxyisoquinoline* (**30**). A solution of **16**, (R = Me, 5·60 g) in conc HCl (50 ml) was warmed to 80° and molten 3,4-dimethoxyphenylglyoxal (7·76 g) was added together with EtOH (20 ml). The mixture was warmed on a water-bath for 30 min, cooled and stored at 0° for 2 days. The crystalline material (3·1 g) was collected and recrystallized from EtOH to yield 4-(3,4-dimethoxyphenacyl)6,7-dimethoxyisoquinoline hydrochloride as colourless needles (2·80 g), m.p. 224–225°; ν_{max} cm^{-1}, 1668 (>CO), 1635 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} (ε) mμ, 240 (48,900), Sh 255 (40, 550), 321 (18,000). (Found: C, 61·35; H, 5·85; N, 3·55; OMe, 28·00. $C_{21}H_{22}NO_5Cl.C_2H_5OH$ requires: C, 61·53; H, 6·27; N, 3·11; OMe, 27·58%.) Basification with ammonia afforded **30**, m.p. 179–180° EtOH) as colourless small prisms in 82% yield; ν_{max} cm^{-1}, 1667 (>CO), 1625 (>C=N—), 1600 (>C=C<); λ_{max} (ε) mμ, 237 (50,600), 277 (16,300), Sh 305 (13,250), Sh 325 (8300) NMR, singlet 8·9 ppm, [1] (C_1), singlet 8·3 ppm, [1] (C_3), singlet 4·5 ppm, [2] (—C*H*$_2$—CO—). (Found: C, 68·26; H, 5·65; N, 4·0. $C_{21}H_{21}NO_5$ requires: C, 68·65; H, 5·76; N, 3·81%.) The base was characterized as the methiodide m.p. 204–205° (dec), pale yellow prisms from EtOH. (Found: C, 51·40; H, 4·74; N, 2·68. $C_{22}H_{24}NO_5I$ requires: C, 51·87; H, 4·75; N, 2·75%.)

2-(3,4-*Dimethoxyphenacyl*)6,7-*dimethoxyisoquinolinium iodide* (**34**). The original hydrochloric acid filtrate from the above experiment was washed with benzene to remove neutral material and then concentrated to small volume when a sticky brown solid separated. Crystallization from EtOH gave eventually a colourless micro-crystalline solid (7·2 g) m.p. 78–80° (with effervescence, resolidification and remelting at 156–160°); ν_{max} cm^{-1}, 3300 (—OH), 1675 (>C=O), 1640 (>C=C<) λ_{max} mμ,

275, 312. NMR (CF_3CO_2H), — identical with that of **34** in the same solvent. NMR (CD_3OD), singlet 8·3 ppm, [1] (C_1), quartet 8·3 ppm [2] $J = 4·5$ c/s. (C_3 and C_4, AB), singlet 5·0 ppm [2] (—CH_2—Ar). Basification of this material, tentatively assigned the structure **35**, gave an unstable oil which rapidly turned red in air. When boiled with HClaq, followed by addition of KIaq the compound, m.p. 78–80°, gave a crystalline iodide salt, which was recrystallized from EtOH to yield very pale yellow prisms, m.p. 189–190°; ν_{max} cm^{-1}, 1690 (>CO), 1640 (>C=$\overset{+}{N}$<), 1615 (>C=C<). λ_{max} (ε) mμ, 280 (19,500), 310 (16,000), NMR (CF_3CO_2H), singlet 9·25 ppm, [1] (C_1), broad singlet 8·9 ppm, [2] (C_3 and C_4), singlet 7·25 ppm, [2] ($\geqslant\overset{+}{N}$—CH_2—Ar). (Found: C, 50·71; H, 4·45; N, 3·06. $C_{22}H_{22}NO_5I$ requires: C, 50·90; N, 4·48; N, 2·83%.)

The iodide was shown to be identical (IR, NMR and mixed m.p.) with **34**, obtained by the interaction of 6,7-dimethoxyisoquinoline with 3,4-dimethoxyphenacyl bromide, followed by anion exchange.

Reduction of the iodide with $NaBH_4$ in aqueous EtOH gave 2-(*β*-hydroxy-3,4-dimethoxyphenylethyl) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, m.p. 122°, as colourless needles from EtOH. (Found: C, 67·71; H, 7·18; N, 4·02. $C_{21}H_{27}NO_5$ requires: C, 67·54; H, 7·29; N, 3·75%.) Methiodide m.p. 190–195° from EtOH. (Found: C, 51·01; H, 6·05; N, 2·69. $C_{22}H_{30}NO_5I$ requires: C, 51·26; H, 5·87; N, 2·72%.)

The secondary alcohol, m.p. 122°, was also obtained by the interaction of 6,7-dimethoxy-1,2,3,4-tetrahydrosioquinoline and 3,4-dimethoxyphenacyl bromide, followed by reduction with $NaBH_4$.

4-(*β-Hydroxy*-3,4-*dimethoxyphenylethyl*) 6,7-*dimethoxyisoquinoline* (**31**). The hydrochloride salt of **30** was suspended in EtOH and treated with an equal weight of $NaBH_4$. After heating for 30 min, the solvent was removed and water added to dissolve the salts; then extraction with benzene afforded, after removal of the dried solvent, a colourless gum which crystallized in contact with ether. Recrystallization from EtOH—ether gave colourless plates (m.p. 75–80°) of **31** (93%). ν_{max} cm^{-1}: ~3350 (OH), 1625 (>C=N—), 1610 (>C=C<); λ_{max} (ε) mμ, 239 (12,900), 282 (2675), 316 (1220). NMR singlet 8·6 ppm, [1] (C_1), singlet 8·0 ppm, [1] (C_3), triplet 4·9 ppm., [1] $J = 7·5$ c/s. (CH_3—CH(OH)—), doublet 3·5 ppm, [2] $J = 7·5$ c/s (CH_2—CH(OH)—). (Found: C, 68·07; H, 6·15; N, 4·01. $C_{21}H_{25}NO_5$ requires: C, 68·28; H, 6·28; N, 3·79%.)

Methiodide, m.p. 203–204°, pale yellow prisms from EtOH. (Found: C, 51·52; H, 5·13; N, 2·80. $C_{22}H_{28}NO_5I$ requires: C, 51·65; H, 5·13; N, 2·74%.)

4-(3,4-*Dimethoxystyryl*) 6,7-*dimethoxyisoquinoline* (**32**). The alcohol **31** (500 mg) was dissolved in $CHCl_3$ (100 ml) and the soln saturated with HCl during 30 min. Removal of the solvent gave a yellow crystalline hydrochloride which was recrystallized from EtOH to yield yellow needles (362 mg), m.p. 213–215°; ν_{max} cm^{-1} 1640, 1620, 1605. (Found: C, 63·52; H, 6·96; N, 3·53. $C_{21}H_{22}NO_4Cl$, C_2H_5OH requires: C, 63·36; H, 6·54; N, 3·21%.)

Basification of the hydrochloride with aqueous ammonia yielded **32** as colourless needles, m.p. 135°, from AcOEt (82% conversion); ν_{max} cm^{-1}, 1635, 1625, 1605. λ_{max} (ε) mμ, 243 (46,600), 336 (25,400). NMR singlet 8·9 ppm, [1] (C_1), singlet 8·5 ppm, [1] (C_3); seven proton multiplet ~7 ppm. (Found: C, 71·60; H, 5·91; N, 4·20. $C_{21}H_{21}NO_4$ requires: C, 71·78; H, 6·02; N, 3·99%.)

2,3,8,9-*Tetramethoxybenzo*[c]*phenanthridine* (**33**). Compd **32** (684 mg) in EtOH (1000 ml) was irradiated for 16 hr in a Hanovia II photochemical reactor. During this time a quantity of insoluble material (150 mg) separated and this was collected. The EtOH was concentrated to low bulk when a further quantity (31 mg) of solid was obtained. The combined crops were purified, first by sublimation at 210–220°/0·1 mm, and then by recrystallization from pyridine. The pure **33**, colourless needles, had m.p. 306–308° (lit.[8] m.p. 302–304°) ν_{max} cm^{-1}, 1615, 1603, λ_{max} (ε) mμ ($CHCl_3$) 285 (30,200), 335 (10,000). (Found: C, 72·39; H, 5·51; N, 4·00; Calc. for $C_{21}H_{19}NO_4$; C, 72·19; H, 5·48; N, 4·01%.)

Evaporation of the ethanolic mother-liquor gave a gummy residue which upon treatment with AcOEt yielded crystalline **32** (421 mg) (61·8% recovery).

4-(3,4-*Dimethoxyphenacyl*) 7,8-*dimethoxyisoquinoline hydrochloride* (**37**). The condensation between 3,4-dimethoxyphenylglyoxal and **22** was carried out essentially as previously described for **30**. The hydrochloride salt was collected and recrystallized from EtOH as pale yellow plates m.p. 212–214° (37%); ν_{max} cm^{-1}, 1669 (>CO), 1645 (>C=$\overset{+}{N}$<), 1618 (>C=C<); λ_{max} (ε) mμ, 233 (40,500), 275 (14,400), 360 (3300). NMR (CF_3CO_2H), doublet 9·7 ppm, [1] $J = 5$ c/s, (C_1), doublet 8·35 ppm,

[1] J = 5 c/s, (C_3), singlet 5·1 ppm, [2] (—CH_2CO—). (Found: C, 62·19; H, 5·60; N, 3·61. $C_{21}H_{21}NO_5HCl$ requires: C, 62·27; H, 5·48; N, 3·46%.)

4-(*β-Hydroxy*-3,4-*dimethoxyphenylethyl*)7,8-*dimethoxyisoquinoline* (38). Reduction of 37 with $NaBH_4$ in EtOH yielded almost quantitatively 38 as a colourless glass which did not crystallise; ν_{max} cm^{-1}, 1625, 1610; λ_{max} mμ, 233, 277, 342, 357. The methiodide was obtained as a pale brown amorphous solid, m.p. 100–102° (from EtOH—ether). NMR singlet 9·5 ppm, [1] (C_1), singlet 8·5 ppm [1] (C_3), singlet 2·6 ppm, [3] (NMe). (Found: C, 51·36; H, 5·04; N, 2·76. $C_{22}H_{26}NO_5I$ requires: C, 51·65; H, 5·13; N, 2·74%.)

4-(3,4-*Dimethoxyphenylstyryl*) 7,8-*dimethoxyisoquinoline* (39). A soln of 38 (500 mg) in $CHCl_3$ (100 ml) was saturated with HCl as described for the prep of 32, and the solvent was then removed to yield 39 as the hydrochloride salt as yellow microprisms m.p. 188–189° (dec) from acetone; ν_{max} cm^{-1}, 1642, 1618, 1608. The free isoquinoline, pale yellow prisms, m.p. 129°, from EtOH, was obtained by basification with aqueous ammonia; ν_{max} cm^{-1}, 1640, 1630, 1605; λ_{max} (ε) mμ, 238 (40,100), 370 (20,410). NMR singlet 9·4 ppm, [1] (C_1), 8·6 ppm [1] (C_3), Complex seven proton multiplet 6·7–7·8 ppm. (Found: C, 71·67; H, 5·90; N, 4·04. $C_{21}H_{21}NO_4$ requires: C, 71·78; H, 6·02; N, 3·99%.)

THE BENZYLATION OF ISOQUINOLINE DERIVATIVES

(Tetrahedron, 1968, 24, 427)

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1,2-DIHYDROISOQUINOLINES—VI[1]

THE BENZYLATION OF ISOQUINOLINE DERIVATIVES[2]

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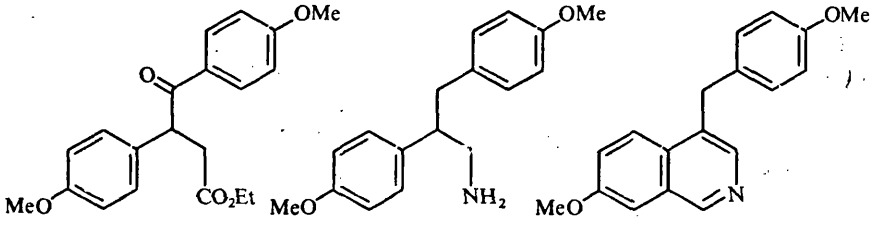
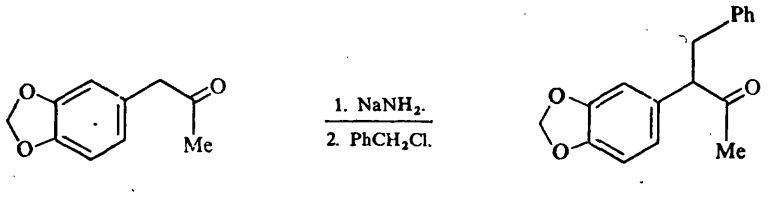
Abstract—Methods of preparation of 4-benzyl-isoquinoline derivatives are briefly reviewed and the condensation of isoquinolinium salts with benzaldehyde under alkaline conditions has been examined; the structure originally proposed by Kröhnke[11] for one of these products has been corrected.

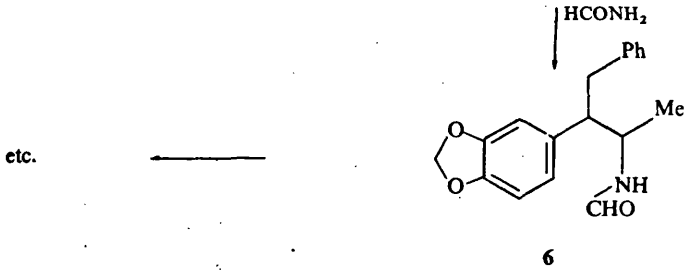
THE methods most usually employed for the synthesis of 4-substituted isoquinoline derivatives have involved the preparation of the appropriately substituted β-arylethylamines, which have then been subjected to the Bischler–Napieralski[3] ring-closure reaction, followed by dehydrogenation. In this way 4-benzylisoquinoline has been prepared[4] in a 6-stage sequence from benzyl cyanide, and Knabe *et al.*[5] have synthesized 1,4-dibenzyl-6,7-dimethoxyisoquinoline in an overall yield of



1 **2** **3**



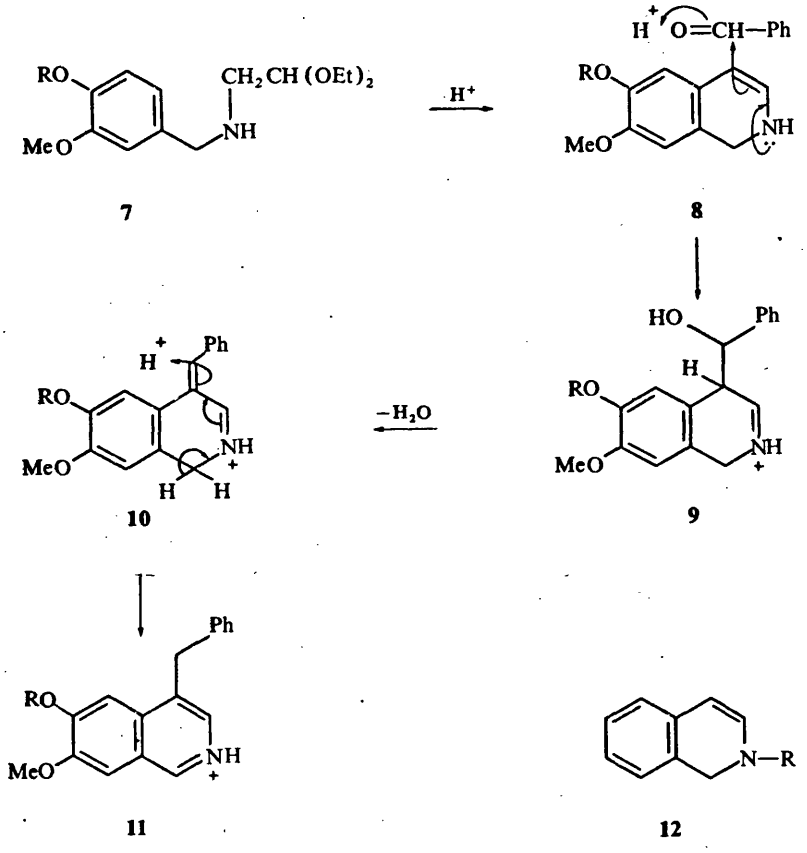
4 **5**



6

18% by the addition of benzyl magnesium bromide to 3,4-dimethoxy-β-nitrostyrene, followed by reduction and ring-closure. The 4-benzylisoquinoline **3** has been obtained[6] by condensing anisoin with ethyl bromoacetate to yield **1**, followed by reduction, conversion to the amine **2**, ring-closure and dehydrogenation; a further variation is provided[7] by the conversion of **4** through **5** to **6**.

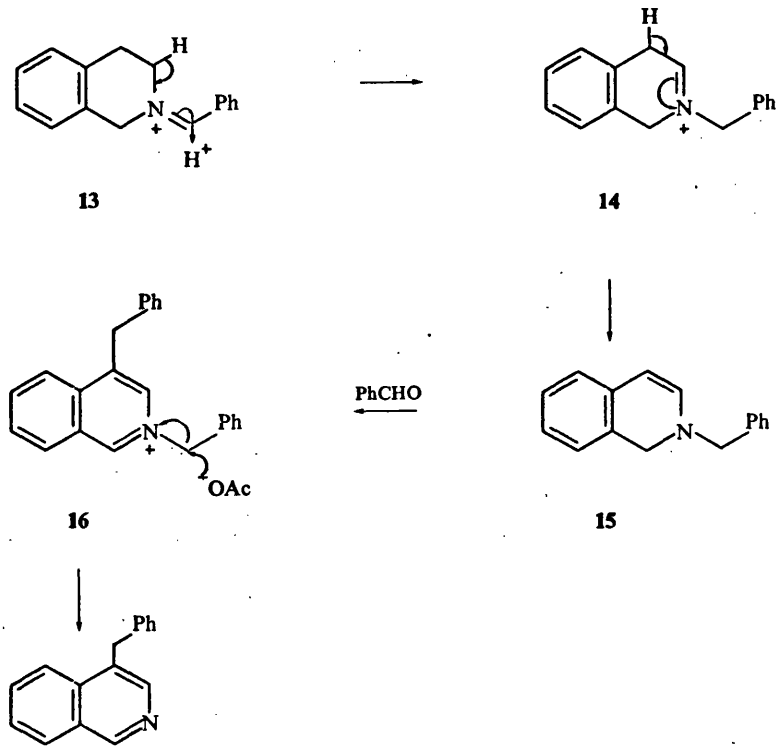
Recently Bobbitt *et al.*[8] have shown that 4-benzylisoquinolines can be obtained simply in good yield by the condensation, in acid solution, of benzaldehyde with phenolic aminoacetals of the type **7** (R = H). The reaction clearly[8] involves the 1,2-dihydroisoquinoline **8** and probably[1,8] proceeds as shown in **8** → **11**. Intermediates of the type **9** have been isolated[1] in some cases.



7 8 9 10 11 12

4-Benzylisoquinoline has been obtained[9] in 34% yield merely by heating a mixture of 1,2,3,4-tetrahydroisoquinoline and benzaldehyde in acetic acid solution. It was suggested[9] that the reaction involves a rearrangement of the originally formed Schiff cation **13** to **14** and then to **15**, which can condense with a second molecule of benzaldehyde in the manner indicated for **8** → **11**, to yield **16**. Finally nucleophilic displacement of the N-benzyl group by acetate anion gives 4-benzylisoquinoline.

We have found that 2-benzyl-1,2-dihydroisoquinoline (**12**, R = CH_2Ph), obtained by reduction of 2-benzylisoquinolinium bromide with LAH, reacts with benzaldehyde in acetic acid solution to give a 40% yield of **16** and, in a separate step, a 12% yield of 4-benzylisoquinoline resulted from heating **16** in acetic acid under the conditions



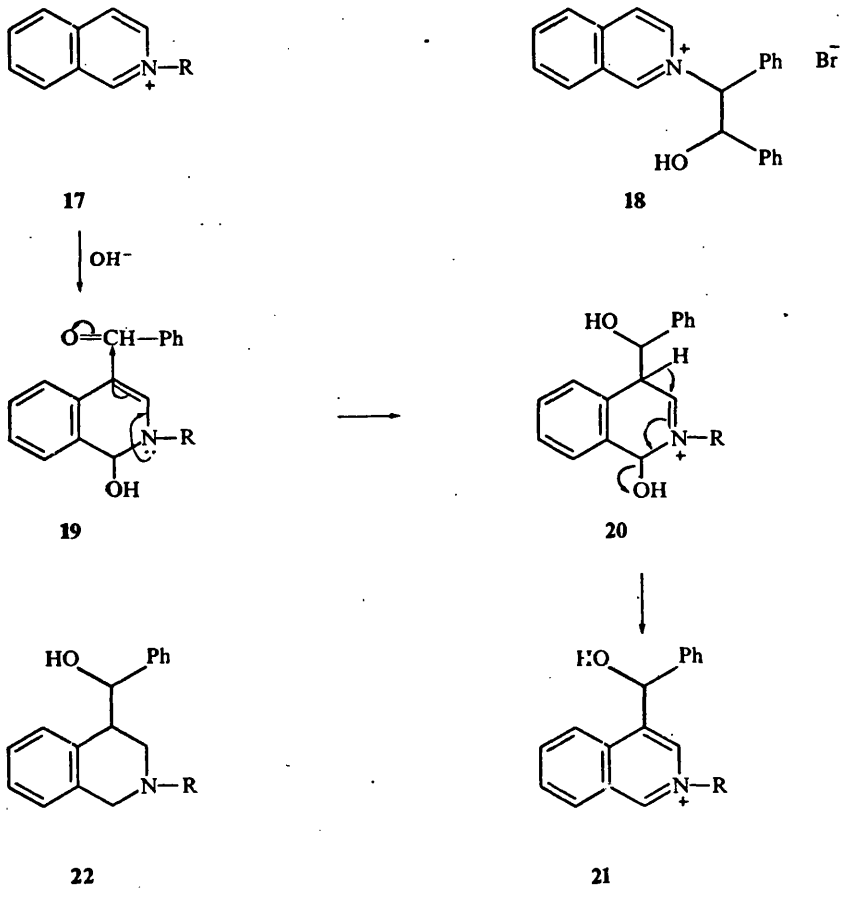
employed by Burrows and Burrows.[9] The yield was increased to 30% by repeating the reaction in the presence of one mole of sodium acetate. Hence, each step in the above mechanism is feasible.

Yet another preparation of 4-benzylisoquinoline, also under acid conditions, has been reported by Grewe *et al.*,[10] who hydrogenated a mixture of isoquinoline and benzaldehyde in acetic acid solution. It was suggested that reduction occurred to give 1,2-dihydroisoquinoline, which then condensed with benzaldehyde to give 4-benzylisoquinoline. The yield was only 13%, and it was difficult to isolate the product in a pure state.

In 1935 Kröhnke[11] reported that benzaldehyde condensed with 2-benzylisoquinolinium bromide (**17**, R = CH_2Ph) in the presence of alkali to yield, after acidification with HBr, an alcohol, m.p. 218° which he formulated as **18** by analogy with previous work[12] in the N-methylpyridine series. Whereas the structure of the pyridine derivative was confirmed by its independent preparation from pyridine and styrene bromohydrin,[12] and later[13] from pyridine and styrene oxide, no structural work was undertaken in the isoquinoline series. It is probable that **17** (R = CH_2Ph) reacts with the alkali to form the pseudobase **19** (R = CH_2Ph) and it occured to us

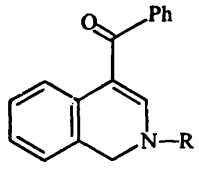
that this may possess some enamine character in alkaline solution. A likely alternative structure for Kröhnke's compound then is **21** (R = CH_2Ph), formed as indicated in **17** → **19** → **20** → **21**.

Accordingly, Kröhnke's directions were repeated and again a quaternary bromide, m.p. 218° was isolated. The UV spectrum was typically that of an isoquinolinium salt, and the presence of a OH group was confirmed by a band at 3250 cm^{-1} in the IR spectrum. The NMR spectrum of the product (taken in CF_3CO_2H with TMS as an



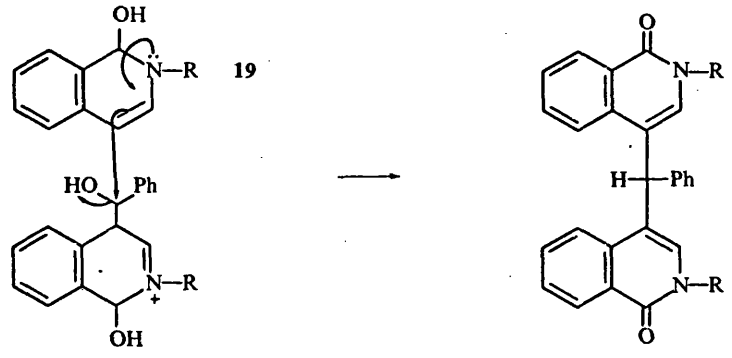
internal standard) was found to be diagnostic for **21** (R = CH_2Ph), with a one proton singlet at 9·7 ppm (C_1–H), and a one proton singlet at 8·9 ppm (C_3–H). Since the latter proton resonates as a singlet, the C_4-position must be substituted. The benzylic methylene group absorbs as a sharp two proton singlet at 6·0 ppm (and at 6·4 ppm in **17** (R = CH_2Ph) itself. Hydrogenation of our compound, m.p. 218° in glacial acetic acid in the presence of Adam's catalyst gave an alcoholic base, m.p. 116°, formulated as **22** (R = CH_2Ph). We have already shown[14] that the interaction of 2-methyl-1,2-dihydroisoquinoline (**12**, R = Me) with aromatic acid chlorides

yields 4-acyl compounds (e.g. **23**, R = Me) and that reduction of these with $NaBH_4$ gives alcohols of the type **22** (R = Me). When 2-benzyl-1,2-dihydroisoquinoline (**12**, R = CH_2Ph) was benzoylated to **23** (R = CH_2Ph), and then reduced, the product (**22**, R = CH_2Ph), m.p. 116° was found to be identical in all respects with the material from the Kröhnke compound.



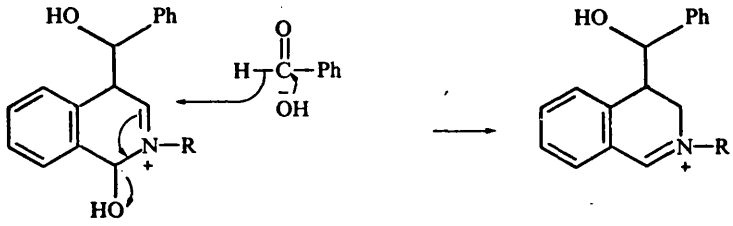
23

By a slight modification of the experimental conditions (Experimental) the Kröhnke reaction yielded a small amount of a neutral compound, m.p. 220°; an elemental analysis and molecular weight determination indicated a dimeric structure. The UV spectrum was suggestive of an isocarbostyril and the IR spectrum exhibited a band at 1665 cm^{-1} consistent with this. The NMR spectrum (taken in $CDCl_3$ with TMS as an internal standard) showed a two proton multiplet centred at 8·47 ppm typical of the C_8-proton in isocarbostyrils, a 16-proton multiplet 6·9–7·45 ppm (aromatic absorption), a two-proton singlet at 6·37 ppm, and one proton singlet at 5·83 ppm and a quartet, integrating for 4 protons, centred at 4·95 ppm, J = 14 c/s. These features are consistent with the structure **24** (R = CH_2Ph), which may be formed as indicated from **19** and **20**, with oxidation occurring during work-up.

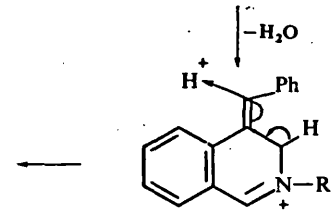


The yield of **21** (R = CH_2Ph) is low (about 10%), and the reaction is a lengthy one, but it does offer a very simple route to 4-substituted isoquinoline derivatives under alkaline conditions, and we decided to investigate the reaction further. Doubling the amount of alkali (to 1·0 mole) resulted in the formation of 2,4-dibenzylisoquinolinium bromide (**16**) in 14% yield, but **21** (R = CH_2Ph) was not isolated. Compound **16** could possibly arise from the initial disproportionation of the pseudobase **19** into 2-benzylisocarbostyril and 2-benzyl-1,2-dihydroisoquinoline—a typical reaction

of isoquinoline pseudobases. The latter **12** (R = CH_2Ph) product could then condense with benzaldehyde and aromatise to **16** in the manner suggested previously. However, since 2-benzylisocarbostyril has not been detected among the products of the condensation, an alternative mechanism for the formation of **16** is summarised in **20** → **25** → **26** → **16** and some support for this process is provided by a study of the condensation of isoquinoline methiodide with benzaldehyde (see below).



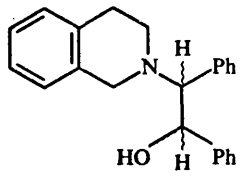
20 **25**



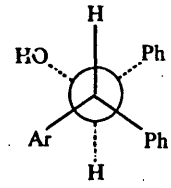
16 **26**

Concentration of the mother liquors from which **16** was obtained gave a quaternary bromide m.p. 240° in low yield. A 70% yield was achieved by condensing 2-benzylisoquinolinium bromide, with benzaldehyde in the presence of one molecular equivalent of sodium ethoxide in ethanol. The UV and IR spectra suggested an isoquinolinium salt containing a OH group, whereas the NMR spectrum (taken in CD_3SOCD_3 with TMS as an internal standard) was consistent with structure **18**, the original proposal by Kröhnke for the first quaternary salt m.p. 218°. In an attempt to confirm this structural assignment, *trans*-stilbene bromohydrin[15] was reacted with isoquinoline in methyiethylketone solution. A crystalline quaternary bromide, m.p. 234° was obtained whose UV, IR and NMR spectra were consistent also with structure **18**, although the substance was clearly not identical with that obtained from the Kröhnke reaction. That the two compounds are diastereomorphs was supported by an examination of the NMR spectra of the 1,2,3,4-tetrahydroisoquinolines **27** derived by reducing these quaternary salts with $NaBH_4$. The tetrahydrobase (m.p. 87°) derived from *trans*-stilbene bromohydrin and isoquinoline would be expected to exist preferentially in the conformation **28a** about the asymmetric centres, whereas its diastereoisomer would exist preferentially in the conformation represented by **28b**.

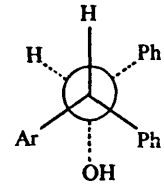
The dihedral angle between the vicinal hydrogen atoms in **28a** is 180° whereas it is only about 60° in **28b**. The hydrogen atoms of the system $\rangle$N—CH(Ph)CH(OH)Ph in the two tetrahydrobases resonate as quartets centred at about 4·3 ppm, but whereas a coupling constant of 10 c/s is observed for the base m.p. 87°, this is reduced to 4 c/s



27

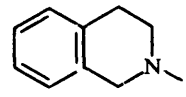


28a

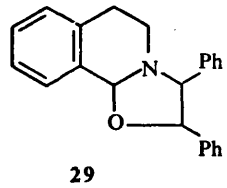


28b

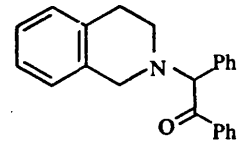
Ar=



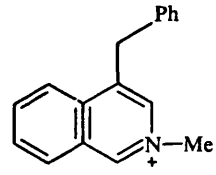
in that base m.p. 126° derived from the product of the Kröhnke reaction. In an attempt to destroy the asymmetry in **27**, the two tetrahydrobases were oxidized, but whereas the m.p. 126° base gave the cyclic ether **29**, the "synthetic" base m.p. 87° yielded the expected ketone **30**, identical with the product obtained from tetrahydroisoquinoline and α-bromodeoxybenzoin.[16] Reduction of **30** regenerated **28a**.



29



30

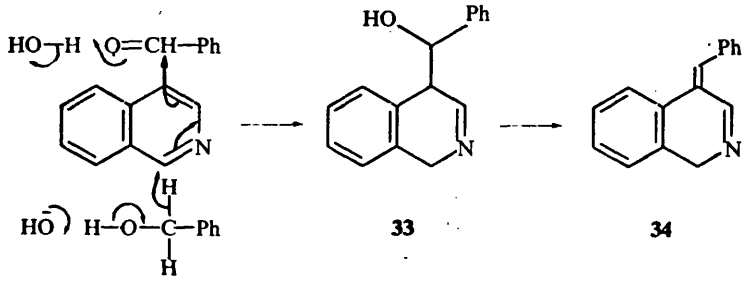


31

When Kröhnke's original conditions were employed with isoquinoline methiodide, the C_4-substituted compound **21** (R = Me) was obtained in 17% yield and its structure was established by methods similar to those used in the 2-benzyl series. With one mole of sodium hydroxide, a new compound was obtained (30%); the spectral characteristics were interpreted in terms of structure **26** (R = Me), and this was supported by heating the substance in methanol solution when isomerism occurred almost quantitatively to **31**, identical with an authentic specimen. A small amount of the dimer **24** (R = Me) was also isolated from the condensation reaction. When ethanolic sodium ethoxide was used in place of aqueous NaOH, a 40% yield

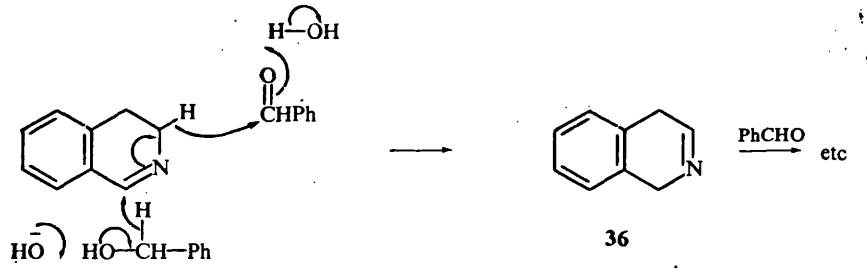
of **26** (R = Me) was obtained. This constitutes the best yield of a 4-substituted isoquinoline so far obtained by us in these reactions, and in view of the simplicity of the procedure, the yields are acceptable for a synthetic method.

If a mixture of isoquinoline, benzyl alcohol and KOH is heated under anhydrous conditions,[17] a 60% yield of 4-benzylisoquinoline results. The reaction is best regarded as proceeding as shown in **32** → **33** → **34** → etc. A 40% yield of 4-benzylisoquinoline is claimed[17] when an anhydrous mixture of 3,4-dihydroisoquinoline,



32 **33** **34**

benzyl alcohol, KOH and benzaldehyde is heated together. The dihydroisoquinoline **35** presumably undergoes a base-catalysed isomerization to **36**, which can then condense with benzaldehyde in a straightforward manner.



35 **36**

One of the best-known reactions of enamines[18] is C-alkylation, and we have now succeeded in benzylating 2-methyl-1,2-dihydroisoquinoline. Since the product, 2-methyl-4-benzyl-1,2-dihydroisoquinoline is expected to be unstable, it was oxidized with iodine, without isolation, to the fully aromatic isoquinolinium salt. The best result, with a 27% yield of 2-methyl-4-benzylisoquinolinium iodide, was obtained with ethanol as a solvent, but the same product was obtained by using isopropanol, isobutanol, dimethylformamide or acetonitrile as solvents.

EXPERIMENTAL

NMR spectra were recorded upon a Varian A-60 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. IR spectra were determined as Nujol mulls upon a Perkin–Elmer 237 instrument and UV spectra were recorded as ethanolic solns upon a Perkin–Elmer 137 spectrophotometer. All m.p. are uncorrected.

2-Benzyl-4(phenylhydroxymethyl)isoquinolinium bromide **21** (R = —CH_2Ph)

10N NaOH (0·36 ml) was added slowly to a soln of N-benzylisoquinolinium bromide (2 g) and benzaldehyde (2 ml) in EtOH (10 ml) containing water (0·5 ml) under N_2. After 5 days the soln was acidified with aqueous 48% HBr soln and stored at 0° for 4 weeks. The pale yellow crystalline product was then collected and recrystallized from EtOH to give **21** (R = CH_2Ph) m.p. 218–220°, yield = 10%. λ_{max} (ε) mμ, 284 (21,800), 340 (2750); ν_{max} cm^{-1}, ~3250 (—OH), 1630 (>C=$\overset{+}{N}$<), 1600 (>C=C<). NMR (CF_3CO_2H) ppm, 9·68 singlet [1] (C_1—H), 8·87 singlet [1] (C_3—H), ~8·2 multiplet [4] (four adjacent aromatic protons), 7·35 singlet [5] (Ph group), 7·50 singlet [5] (Ph group), 6·00 singlet [2] (>N—CH_2—Ph). (Found: C, 67·62; H, 5·10; N, 3·30. $C_{23}H_{20}NOBr$ requires: C, 68·00; H, 5·00; N, 3·50%.)

2-Benzyl-4(phenylhydroxymethyl)1,2,3,4-tetrahydroisoquinoline **22** (R = CH_2Ph)

Method 1. Compound **21** (R = CH_2Ph; 0·5 g) in glacial AcOH (15 ml) was hydrogenated at 2 atm press over Adam's catalyst overnight. After removal of the catalyst the soln was basified and the ppt extracted into ether; removal of the solvent gave an oil which crystallized upon trituration with EtOH. Recrystallization of this product from EtOH afforded colourless prisms (0·3 g) m.p. 116°. λ_{max} (ε) mμ, 265 (3700); ν_{max} cm^{-1}, ~3200 (—OH). (Found: C, 84·3; H, 6·9; N, 8·3. $C_{23}H_{22}NO$ requires: C, 84·1; H, 6·8; N, 8·0%.)

Method 2 *via compound* **23** (R = —CH_2Ph). Dry 2-benzylisoquinolinium bromide (11 g) was suspended in dry ether (200 ml) and LAH (3 g) cautiously added: after stirring for 2 hr the excess reagent was destroyed by the addition of 33% sodium potassium tartrate aq. The ethereal soln of the 1,2-dihydroisoquinoline thus obtained was decanted quickly from the ppt and protected under N_2. Et_3N (5 ml) was then introduced and benzoyl chloride (6 ml) added dropwise. A yellow product, contaminated with Et_3NHCl, rapidly formed, this was collected, washed firstly with ether then with water and finally recrystallized from $CHCl_3$ to yield 2-benzyl-4-benzoyl-1,2-dihydroisoquinoline (19%) m.p. 133–134°; λ_{max} (ε) mμ, 227 (18,700), 307 (11,900), 350 (13,050); ν_{max} cm^{-1}, 1620, 1610 (>C=C<), 1585 (>C=O). NMR ($CDCl_3$) ppm 8·68 multiplet [1] (aromatic proton *ortho* to >C=O), 4·08 singlet [2] and 4·33 singlet [2] (benzylic $\underline{CH_2}$ groups). (Found: C, 85·0; H, 6·1; N, 4·5. $C_{23}H_{19}NO$ requires: C, 84·9; H, 5·9; N, 4·3%.)

This material (1 g) was dissolved in 90% EtOH and treated with $NaBH_4$. After heating on a water-bath for 1 hr the solvent was removed and water (10 ml) added. Extraction of the ppt into ether gave, after removal of the ether, a colourless solid which recrystallized from EtOH, yielding small prisms (0·82 g) m.p. 115–116°, identical in every respect with the material obtained in method 1 above.

2,4-Dibenzylisoquinolinium bromide (**16**)

10N NaOH (2 ml) was added slowly to a soln of 2-benzylisoquinolinium bromide (6 g) and benzaldehyde (6 ml) in EtOH (30 ml) containing water (2 ml). After 5 days at R.T. under N_2, 48% HBr aq was added until acid to litmus. EtOH (10 ml) was then introduced and the reaction mixture cooled to 0°, whereupon pale brown crystals of 2,4-dibenzylisoquinolinium bromide (0·98 g) separated. Recrystallization from EtOH yielded almost colourless prisms (m.p. 178–179°). (Found: C, 67·60; H, 5·68; N, 3·32; Br, 20·10. $C_{23}H_{20}NBr$, H_2O requires: C, 67·60; H, 5·39; N, 3·43; Br, 19·57%.)

Debenzylation of 2,4-dibenzylisoquinolinium bromide

2,4-Dibenzylisoquinolinium bromide (5 g), glacial AcOH (30 ml) and AcONa (1.37 g) in dry toluene were heated under reflux for 20 hr. After removal of a small quantity of insoluble material, the cooled filtrate was extracted with 2N HCl (3 × 20 ml). Basification and ether extraction of the combined acid washings gave 4-benzylisoquinoline, m.p. 115–117°, (lit.[19] 118°) identical with an authentic specimen, yield 30%.

The dimeric isocarbostyril **24** (R = CH_2Ph)

10N NaOH (0·36 ml) was added slowly to a soln of N-benzylisoquinolinium bromide (2 g) and benzaldehyde (2 ml) in EtOH (10 ml) containing water (0·5 ml) under N_2. After 5 days the soln was acidified with aqueous 48% HBr soln and set aside for 7 days at 0°. Some crystals of NaBr were removed and the EtOH

evaporated. After a further period of 6 days at 0° some yellow crystals (0·6 g) were obtained* which were recrystallized firstly from EtOHaq and then from EtOH–$CHCl_3$ to give colourless prisms, m.p. 220–221°; λ_{max} (ε) mμ, 297 (4470), 331 (2600); ν_{max} cm^{-1}, 1660 (ArCON<), 1630 (>C=C<). NMR ($CDCl_3$) ppm, 8·45 multiplet [2] (aromatic protons *ortho* to carbonyl), 6·36 singlet [2] (>C<u>H</u>—N<), 4·76 quartet [4] J = 14 c/s (>N—C<u>H</u>$_2$—Ph). (Found: C, 83·67; H, 5·33; N, 5·21; M.W. 525. $C_{33}H_{26}N_2O_3$ requires: C, 83·85; H, 5·41; N, 5·01%; M.W. 558.)

1,2-Diphenyl-2(N-isoquinolinium)1-hydroxyethane bromide (**18**)

Concentration of original mother-liquor, from which **16** had separated, gave an oil which, upon addition of ether, yielded a second quarternary bromide (1·36 g). Recrystallization of this material from EtOH gave pale yellow prisms†, m.p. 240–241°; λ_{max} (ε) mμ, 236 (50,900), 282 (5100), 341 (4200); ν_{max} cm^{-1}, 3230 (—OH), 1647 (>C=$\overset{+}{N}$<), 1610 (>C=C<). NMR (CD_3SOCD_3) ppm 11·1 singlet [1] (C_1—<u>H</u>), 9·4 doublet [1] J = 8 c/s (C_3—<u>H</u>), 6·65 quartet [2] J = 10·5 c/s (>N—C<u>H</u>Ph—C<u>H</u>(OH)Ph), 3·7 broad singlet [1] (O<u>H</u>—). (Found: C, 68·00; H, 5·08; N, 3·66; Br, 19·79. Calc. for $C_{23}H_{20}NOBr$: C, 68·29; H, 4·96; N, 3·45; Br, 19·67%)

1,2-Diphenyl-2-(N-1,2,3,4-tetrahydroisoquinolyl)1-hydroxyethane (**27**)

1,2-Diphenyl-2-(N-isoquinolinium)1-hydroxyethane bromide (4·1 g) prepared in the previous experiment was dissolved in 90% aqueous EtOH and reduced with $NaBH_4$ (2 g). Removal of the solvent and addition of water gave a solid, which was collected and recrystallized from EtOH to give colourless needles (2·6 g) m.p. 121–122°. NMR ($CDCl_3$) ppm 3·5 quartet [2] J = 4 c/s (>N—C<u>H</u>(Ph)C<u>H</u>(OH)Ph), ~3·2 broad singlet [1] removed with D_2O (<u>H</u>O—), 2·65 singlet [2] (PhC<u>H</u>$_2$—N<). (Found: C, 83·85; H, 7·00; N, 4·21. $C_{23}H_{23}NO$ requires: C, 83·85; H, 7·04; N, 4·25%.)

The cyclic ether **29**

1,2-Diphenyl-2-(N-1,2,3,4-tetrahydroisoquinolyl)1-hydroxyethane (1·2 g) in acetone (150 ml) was shaken with MnO_2 (10 g) for 45 hr, then filtered and the solvent removed to yield a yellow oil. Trituration with EtOH and recrystallization from this solvent eventually gave stout colourless needles (0·45 g), m.p. 101–108°. The IR spectrum indicated the absence of OH and CO functions and the NMR in $CDCl_3$ revealed a two proton quartet J = 7·0 c/s centred at 4·25 ppm characteristic of the two adjacent exocyclic protons of the ethane residue. The combined evidence above is best accommodated by the expression **27**; λ_{max} (ε) mμ, 265 (846). (Found: C, 84·07; H, 6·42; N, 4·58. $C_{23}H_{21}NO$ requires: C, 84·37; H, 6·46; N, 4·28%.)

2,4-Dibenzylisoquinolinium iodide

Method 1. Compound **15** in ether (200 ml), prepared by the reduction of 2-benzylisoquinolinium bromide (10 g) with LAH, was treated with glacial AcOH (25 ml) and benzaldehyde (3·5 g). The red coloured soln thus formed was heated under reflux, in a protective atmosphere of N_2, for 2 hr and then stood at R.T. for a further 56 hr. Removal of the solvents gave a dark red oil which was diluted with water and extracted with ether. Evaporation of the aqueous phase afforded a dark viscous oil which when treated with sat KIaq yielded crystals of **16**. Recrystallization from a small volume of water gave yellow needles (4·5 g) m.p. 185–189°. Further recrystallization from $CHCl_3$–Et_2O raised the m.p. to 197–199°.

Method 2. EtONa (1·36 g) in EtOH (20 ml) was added slowly to a soln of 2-benzylisoquinolinium bromide (6 g) in EtOH, protected by an atm of N_2. After 10 min a fine ppt of NaBr (1·04 g), which had formed,

* A small quantity of **18** was obtained upon concentration of the mother-liquor from which **24**(R = CH_2Ph) was separated.

† This same compound was also prepared in the following manner, this time however no 2,4-dibenzylisoquinolinium bromide was isolated:

EtONa (2·27 g) in EtOH (50 ml) was added to a suspension of 2-benzylisoquinolinium bromide (10 g) in benzaldehyde (10 ml) under N_2. After 10 days the mixture was acidified with 48% HBraq and cooled to 0°; during a further 24 hr yellow crystals (8·3 g) separated, these were collected. Concentration of the mother-liquor gave a further crop (2·3 g). The combined yield of **18** was 62%, m.p. 240–241° from EtOH.

was removed and benzyl bromide (7 ml) in EtOH (10 ml) was introduced. After shaking for 48 hr and standing for a further 3 days, 48% HBr aq (7 ml) was added and the reaction mixture cooled to 0°. A further quantity of NaBr (0·52 g) was removed and the filtrate stored at 0° for 2 days. During this time brown crystals formed; these were collected and recrystallized from EtOH to yield 2,4-dibenzylisoquinolinium bromide as colourless prismatic needles (1·4 g) m.p. 178–179°. Treatment of this compound as a conc soln in water with KI gave the corresponding iodide m.p. 197–199° identical in every respect with the material obtained in the previous experiment, Method 1.

Attempted synthesis of structure **18**

A mixture of the bromohydrin (6·7 g), from *trans*-stilbene, and isoquinoline (4·8 g) were dissolved in MeCOEt and heated under reflux for 48 hr. After cooling the crystalline product was collected and recrystallized from EtOH as colourless prisms (3·0 g) m.p. 234–235°. λ_{max} (ε) mμ, 236 (60,500), 283 (5100), 341 (4000); ν_{max} cm^{-1}, 3250 (—OH), 1650 (>C=$\overset{+}{N}$<), 1613 (>C=C<). NMR (CD_3SOCD_3) ppm 10·90 singlet [1] (C_1—H), 9·15 doublet [1] J = 7·5 c/s (C_3—H), 6·53 quartet {2] J = 8·0 c/s (>N—CH(Ph)—CH(OH)Ph), ~3·5 broad singlet [1] (—OH). (Found: C, 68·10; H, 5·02; N, 3·65. $C_{23}H_{20}NOBr$ requires: C, 68·29; H, 4·96; N, 3·45%.) This compound was reduced with $NaBH_4$ in the usual way to give a tetrahydrobase, m.p. 87–91°. NMR ($CDCl_3$) ppm 4·2 quartet [2] J = 10 c/s (>N—CH(Ph)CH(OH)Ph), ~2·25 singlet [1] (—OH removed by deuteration). (Found: C, 83·65; H, 6·95; N, 4·10. $C_{23}H_{23}NO$ requires: C, 83·85; H, 7·04; N, 4·25%.)

1,2-*Diphenyl*-2-(N-*isoquinolinium*)1-*ketoethane bromide*

A mixture of α-bromodeoxybenzoin (4 g) and isoquinoline (3·9 g) in MeCOEt (30 ml) was heated on a steam-bath for 30 min. After cooling a pale brown coloured ppt was collected and recrystallized from EtOH affording a colourless micro-crystalline solid (95%), m.p. 233–234°; λ_{max} (ε) mμ, 286 (40,300), 343 (3800); ν_{max} cm^{-1}, 1690 (>CO), 1645 (>C=$\overset{+}{N}$<), 1605 (>C=C<). NMR (CF_3CO_2H) 9·4 singlet [1] (C_1—H), 8·04 quartet [2] J = 8 c/s (C_3—H, C_4—H). (Found: C, 68·34; H, 4·62; N, 3·79; Br, 20·08. $C_{23}H_{18}NOBr$ requires: C, 68·60; H, 4·49; N, 3·47; Br, 19·76%.) Hydrogenation at 2 atm press in EtOH over Adam's catalyst gave a tetrahydrobase m.p. 87–90° identical in every respect with the compound obtained above.

2-(N-1,2,3,4-*tetrahydroisoquinolyl*)*phenylbenzyl ketone* **30**

Oxidation of the tetrahydrobase m.p. 87° (0·8 g) with MnO_2 in acetone gave, after removal of reagent and solvent, a brown gum which crystallized upon treatment with EtOH. Recrystallization from EtOH afforded colourless prisms (0·11 g) m.p. 128–129°. NMR ($CDCl_3$) ppm ~7·6 multiplet [2] (aromatic protons *ortho* to carbonyl), 4·95 singlet [1] (>N—CH(Ph)R), 3·65 singlet [2] (Ar—CH_2—N<), 2·75 broad singlet [4] (Ar—CH_2—CH_2—N<). (Found: C, 84·27; H, 6·41; N, 4·12. $C_{23}H_{21}NO$ requires: C, 84·37; H, 6·47; N, 4·28%.)

4-*Benzyl*-2-*methylisoquinolinium iodide* **31**

Method 1. 2-Methyl-1-2-dihydroisoquinoline, from isoquinolinium methiodide (10 g), in ether (250 ml) was treated with approximately an equimolar quantity of benzyl bromide and Et_3N dissolved in EtOH* (100 ml). After heating under N_2 at reflux for 4 hr, most of the ether was removed and AcOK (4 g) introduced. I_2 in warm EtOH was then added until the I_2 colour persisted and the period of heating continued for a further 30 min. After cooling excess I_2 was destroyed with SO_2 and the volume of the soln reduced to ca. 30 ml; water (100 ml) was then added and the reaction mixture extracted with $CHCl_3$ (3 × 30 ml). Evaporation of the combined $CHCl_3$ extracts gave a red gum which crystallized on trituration with EtOH. Recrystallization from EtOH gave pale yellow needles m.p. 185–186° (lit.[20] 188°), yield 27%. (Found: C, 56·66; H, 4·67; N, 3·73. Calc. for $C_{17}H_{16}IN$: C, 56·54; H, 4·46; N, 3·88%.)

* Repetition of this procedure using solvents other than EtOH gave the following results: Acetonitrile 9% isopropanol 15% dimethylformamide 8% isobutanol 13% dioxan 0%.

Method 2. Isoquinolinium methiodide (8·1 g) in EtOH (30 ml) containing benzaldehyde (8 ml) was treated with 10N NaOH (1·65), water (1·5 ml) and EtOH (10 ml). After shaking for 24 hr under N_2, the reaction mixture was set aside for 4 days; then acidified with HI aq and cooled to 0°. The crystalline product was collected and recrystallized from MeOH to give pale yellow rosettes, (1·90 g) m.p. 205–206°; a mixed m.p. with material from method 1 above caused no depression; λ_{max} (ε) mμ, 280, 340; ν_{max} cm^{-1}, 1645 (>C=N<), 1610 (>C=C<), NMR (CF_3CO_2H) ppm 8·68 singlet [1] (C_1—H), 8·50 singlet [1] (C_3—H), 5·20 singlet [2] (—CH_2Ph), 3·89 singlet [3] (>N—CH_3).

Method 3. Isoquinolinium iodide (8·1 g) and benzaldehyde (8 ml) in EtOH (30 ml) were heated with EtONa (3·06 g) in EtOH (20 ml) under N_2. After 5 days the dark red soln was acidified with HI aq and cooled to 0°. The crystalline product which formed was collected and recrystallized from MeOH to give deep yellow needles (5·0 g) m.p. 151–153°; λ_{max} (ε) mμ, 265, 370; ν_{max} cm^{-1}, 1660 (>C=N<), 1595 (>C=C<). NMR (CD_3SOCD_3) ppm, 10·1 singlet [1] (C_1—H), 4·58 singlet [2] (—CH_2—N<), 4·55 singlet [3] (>N—CH_3). (Found: C, 56·69; H, 4·46; N, 3·95; I, 35·25. $C_{17}H_{16}NI$ requires: C, 56·54; H, 4·46; N, 3·88; I, 35·14%.)

Repeated recrystallization from MeOH caused an obvious change to occur yielding a much lighter coloured product m.p. 203–205°; this proved to be identical with the product prepared in Method 2.

The mother-liquor from which the deep yellow product m.p. 151–153° originally separated was evaporated almost to dryness and the residue chromatographed upon alumina. After a fore-fraction containing benzaldehyde, benzene eluted a colourless crystalline material (24, R = Me), which recrystallized from EtOH–$CHCl_3$ mixtures, yield 0·6 g, m.p. 279–280°; λ_{max} (ε) mμ, 287, 326; ν_{max} cm^{-1}, 1650 (Ar—CO—N<) 1625 (>C=C<). NMR ($CDCl_3$) ppm, 8·45 multiplet [2] (aromatic protons adjacent to carbonyl), 6·5 singlet [2] (>CH—N<), 5·96 [1] (>CH—Ph). (Found: C, 80·06; H, 5·37; N, 6·75. $C_{27}H_{22}N_2O_2$ requires: C, 79·78; H, 5·46; N, 6·89%.)

2-Methyl-4-(phenylhydroxymethyl)isoquinolinium iodide (21, R = Me)

Isoquinolinium methiodide (8·1 g) in a mixture of benzaldehyde (8 ml) and EtOH (30 ml) was treated under a protective N_2 atm with 10N NaOH (1·65 ml), water (1·5 ml) and EtOH (10 ml). After shaking for 24 hr and standing for 4 days at 0° the yellow crystalline product was collected by filtration and recrystallized from MeOH (1·92 g) m.p. 205–206°; λ_{max} (ε) mμ, 279, 338; ν_{max} cm^{-1}, 3300 (OH), 1645 (>C=N<), 1610 (>C=C<). NMR (CD_3SOCD_3) ppm, 9·80 singlet [1] (C_1—H), 8·80 singlet [1] (C_3—H), 6·60 singlet [1] (OH removable by deuteration), 6·53 singlet [1] (Ph—CH(OH)—), 4·61 singlet [3] (—NCH_3). (Found: C, 54·21; H, 4·17; N, 3·64; I, 33·60. $C_{17}H_{16}NO_4I$ requires: C, 54·14; H, 4·28; N, 3·71; I, 33·65%.)

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NEW SYNTHESES OF AVICINE AND NITIDINE DERIVATIVES

(Tetrahedron, 1968, 24, 1467)

Tetrahedron. Vol. 24, pp. 1467 to 1474. Pergamon Press 1968. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—VII[1]

NEW SYNTHESES OF AVICINE AND NITIDINE DERIVATIVES

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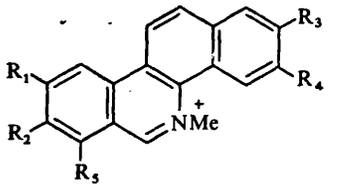
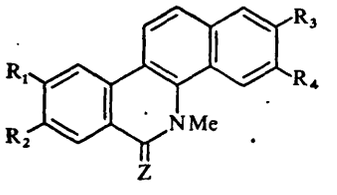
Abstract—Synthetic routes to the benzo[c]phenanthridine ring system have been investigated, and new syntheses of oxyavicine (**2a**), 2,3-dimethoxy-8,9-methylenedioxybenzo[c]phenanthridine (**5c**) and 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**) are described.

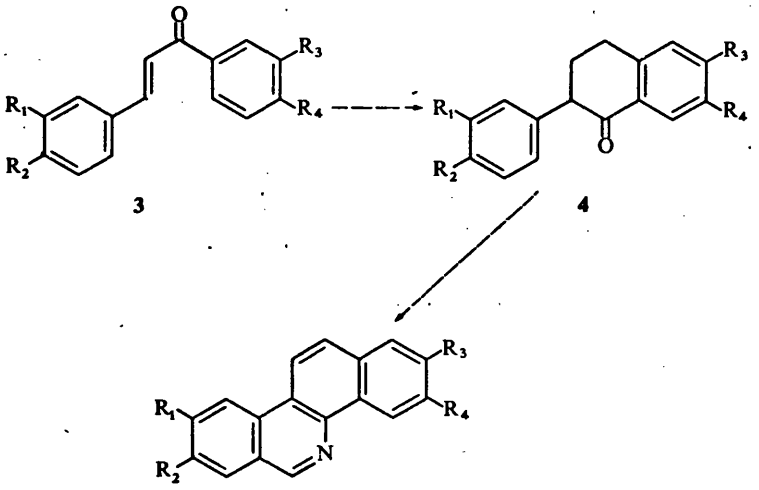
THE benzo[c]phenanthridine alkaloids avicine (**1a**) and nitidine (**1b**) were isolated and characterized by Arthur *et al.*[2] who found that they readily disproportionate into the oxy-forms (**2a** and **2b**) and the corresponding dihydro derivatives (**2c** and **2d**) respectively. Syntheses of oxyavicine (**2a**)[3] and dihydronitidine (**2d**)[4] have been reported by essentially the same method as established by Bailey *et al.*[5] in their synthesis of chelerythrine (**1c**). In this method the necessary chalcone (**3**) was converted via the 2-aryl-1-tetralone (**4**) into the fully aromatic benzo[c]phenanthridine (**5**), which was then N-methylated and either oxidized to oxyavicine (**2a**) or reduced to dihydronitidine (**2d**). Some other oxygenated benzo[c]phenanthridines (**5**) have also been prepared[6] by this method.



1a $R_1, R_2 = R_3, R_4 = CH_2O_2$; $R_5 = H$.
1b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$; $R_5 = H$.
1c $R_2 = R_5 = OMe$; $R_3, R_4 = CH_2O_2$; $R_1 = H$.



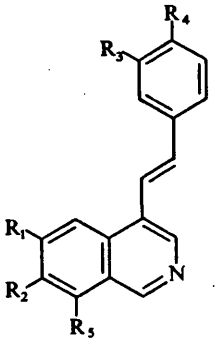
2a $R_1, R_2 = R_3, R_4 = CH_2O_2$; $Z = O$.
2b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$; $Z = O$.
2c $R_1, R_2 = R_3, R_4 = CH_2O_2$; $Z = H_2$.
2d $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$; $Z = H_2$.



3 4

5a $R_1 = R_2 = R_3 = R_4 = OMe$.
5b $R_1, R_2 = R_3, R_4 = CH_2O_2$.
5c $R_1 = R_2 = OMe$; $R_3R_4 = CH_2O_2$.
5d $R_1 = R_2 = R_3 = R_4 = H$.

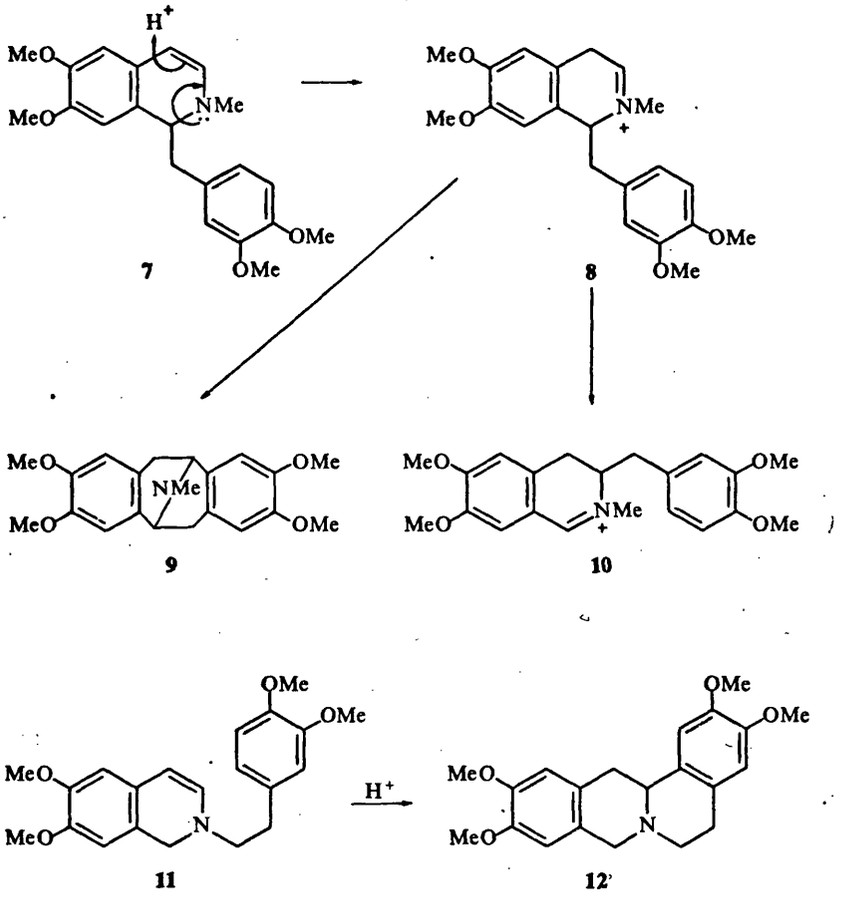
In Part V of this series[7] we described an efficient method for the synthesis of styrenes of the type **6**, which were required for attempted photochemical ring closure to the benzo[c]phenanthridine ring system. We had hoped, in view of the high overall yield of 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**) obtained by the photolysis of the styrene (**6a**), that this synthetic route might prove to be of general value in the preparation of the alkaloids of this group. However, the unsymmetrically substituted styrenes (**6c** and **6d**) have so far proved to be very difficult to cyclise under our conditions and so we have sought alternative synthetic routes to the benzo[c]-phenanthridine ring system.



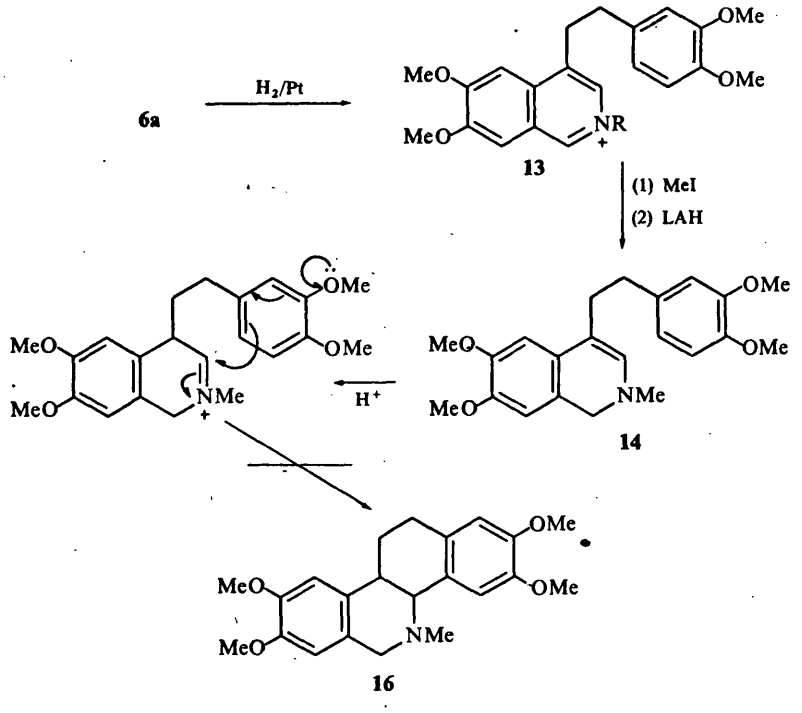
6a $R_1 = R_2 = R_3 = R_4 = OMe$; $R_5 = H$.
6b $R_1, R_2 = R_3, R_4 = CH_2O_2$; $R_5 = H$.
6c $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$; $R_5 = H$.
6d $R_2 = R_3 = R_4 = R_5 = OMe$; $R_1 = H$.

It is well-known that when a 1,2-dihydroisoquinoline, for example **7**, is treated with mineral acid the C_4-protonated form **8** that results is susceptible to nucleophilic

attack at C_3. Examples of such reactions are provided by the formation of N-methylpavine[8] (9), from 7, the rearrangement of 7 to the 3-benzyl-3,4-dihydroisoquinolinium salt[9] (10), and the formation of the berbine skeleton, for example 12 from the N-(β-arylethyl)-1,2-dihydroisoquinoline (11).[10]

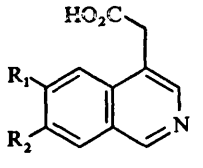


It seemed to us that an analogous synthesis of the benzo[c]-phenanthridine ring system should be possible from a suitably substituted 4-(β-arylethyl)-1,2-dihydroisoquinoline (**14** → **16**), and to test this hypothesis we chose the derivative **14**. This was readily prepared by the catalytic hydrogenation of the styrene **6a** to **13**, (R = H), followed by reduction of the methiodide with LAH. Although the conditions of acid treatment were varied over wide limits, the only observable reaction of the dihydroisoquinoline (**14**) was disproportionation into **13**, (R = Me) and the corresponding 1,2,3,4-tetrahydroisoquinoline. In our experience such a disproportionation occurs extremely readily with 4-substituted -1,2-dihydroisoquinolines.

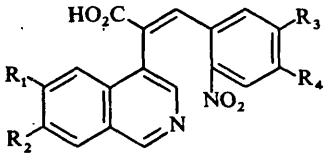


In 1963 Abramovitch and Tertzakian[11] described a new synthesis of benzo[c]-phenanthridine itself (**5d**) that involved the condensation of 4-isoquinolylacetic acid (**17c**) with *o*-nitrobenzaldehyde, reduction of the resulting *cis*-styrene **18d** to the amino acid **19d** followed by a Pschorr-type ring-closure to **20d** and final decarboxylation to **5d**. Unfortunately the starting material **17c** was only available in an 8-stage sequence from isoquinoline, and hence this otherwise attractive route to the benzo[c]-phenanthridines was not further studied.

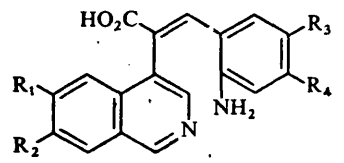
It has been shown[12] that benzaldehyde may be condensed with aminoacetals of the type **21** (R_3 = H) to yield 4-benzylisoquinoline derivatives, and we have examined a large number of other aldehydes in this reaction.[13] We have now found that glyoxylic acid will react with these aminoacetals to yield an easily separable mixture of the corresponding 2- and 4-isoquinolylacetic acids in good yield. By using the N-methyl-aminoacetals **21** (R_3 = Me) yields of the 4-isoquinolylacetic acids approaching



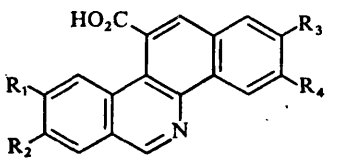
17a $R_1, R_2 = CH_2O_2$.
17b $R_1 = R_2 = OMe$.
17c $R_1 = R_2 = H$.



18a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
18b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$.
18c $R_1 = R_2 = R_3 = R_4 = OMe$.
18d $R_1 = R_2 = R_3 = R_4 = H$.

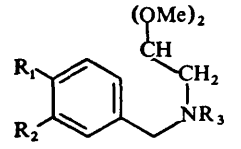


19a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
19b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$.
19c $R_1 = R_2 = R_3 = R_4 = OMe$.
19d $R_1 = R_2 = R_3 = R_4 = H$.

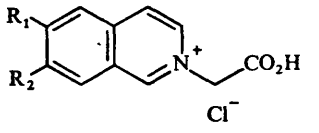


20a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
20b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$.
20c $R_1 = R_2 = R_3 = R_4 = OMe$.
20d $R_1 = R_2 = R_3 = R_4 = H$.

90% have been realized. We have thus been able to examine further the scope of the Abramovitch and Tertzakian route to the benzo[c]phenanthridines and report here new syntheses of oxyavicine (**2a**), 2,3-dimethoxy-8,9-methylenedioxybenzo[c]-phenanthridine (**5c**) and 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**).



21a $R_1, R_2 = CH_2O_2$; $R_3 = H$.
21b $R_1 = R_2 = OMe$; $R_3 = H$.



22a $R_1, R_2 = CH_2O_2$

The interaction of the aminoacetal **21a** with glyoxylic acid in HCl solution gave the 4-isoquinolylacetic acid (**17a**) in 68% yield, together with small amounts of the N-substituted isoquinolinium salt (**22a**). Condensation of **17a** with 6-nitropiperonal produced a 74% yield of the styrene **18a** which was reduced with ammoniacal ferrous sulphate to **19a** (60%). Ring-closure of **19a**, essentially as described by Abramovitch and Tertzakian[11] gave **20a**, which, without isolation was decarboxylated thermally to 2,3,8,9-bismethylenedioxybenzo[c]phenanthridine (**5b**). The overall yield of **5b** *from piperonal* was 5%. Finally N-methylation of **5b**, followed by oxidation yielded oxyavicine, identical with an authentic specimen derived[2] from the natural product.

Repetition of the above synthetic sequences with 4-(6,7-dimethoxyisoquinolyl)acetic acid (**17b**) and 6-nitropiperonal gave 2,3-dimethoxy-8,9-methylenedioxybenzo[c]-phenanthridine (**5c**) identified by comparison with an authentic sample.[3]

Finally by using 6-nitroveratraldehyde with **17b**, 2,3,8,9-tetramethoxybenzo[c]-phenanthridine (**5a**) was produced, identical with a sample prepared[7] by photochemical ring-closure of the styrene **6a**.

EXPERIMENTAL

Mps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are measured in ppm downfield from TMS as an internal standard.

6,7-Dimethoxy-4-(3,4-dimethoxyphenylethyl)isoquinolinium methiodide (**13**). The styrene **6a** in HCl aq was treated with a molar equiv of $NaClO_4$ in water, and the immediate yellow ppt collected and crystallized from aqueous acetone as needles, m.p. 241–242°, yield 92%; λ_{max} mμ, (ε) 265 (26,900), 350 (10,800), ν_{max} cm^{-1}, 1645 (>C=N<), 1610, 1595 (>C=C<), 1110 (ClO_4^-). (Found: C, 54·3; H, 5·3; N, 3·3. $C_{22}H_{24}NO_8Cl$ requires: C, 54·6; H, 5·4; N, 2·90%.)

This perchlorate (0·2 g) was dissolved in acetone (30 ml) containing water (4 ml) and 1 drop $HClO_4$ (60%) and hydrogenated at 2 atm press over Adam's catalyst (0·02 g) for 6 hr. After removal of the catalyst the acetone was evaporated and the residue cooled to 0°. Collection of the solid product and crystallization from EtOH yielded very pale yellow prisms (0·16 g) m.p. 216–217°; λ_{max} mμ, (ε) 257 (56,200); 318 (11,650); ν_{max} cm^{-1}, 1655 (>C=N<), 1635, 1620, 1600 (>C=C<), 1100 (ClO_4^-); NMR (CF_3CO_2H) ppm, 8·9 doublet [1] J = 5·5 c/s (C_1—H), 7·85 doublet [1] J = 5·5 c/s (C_3—H) 7·5 singlet [1], 7·25 singlet [1], (C_5—H) (C_8—H) ~6·60 complex [3], ~3·30 complex [4] (Ar—CH_2CH_2—). (Found: C, 55·6; H, 5·4; N, 3·2. $C_{21}H_{24}NO_4$, ClO_4 requires: C, 55·5; H, 5·3; N, 3·1%.)

• Basification of this material with ammonia gave the free isoquinoline as a pale yellow gum which crystallized on trituration with ether and recrystallized from EtOH as imperfect cubes m.p. 118–120°, yield 82%; λ_{max} mμ, (ε) 240 (32,450), 281 (4570), 313 (2500), 328 (2710). ν_{max} cm^{-1}, 1625 (>C=N<) 1615, 1590 (>C=C<); NMR ($CDCl_3$) ppm, 8·6 singlet [1] (C_1—H), 7·9 singlet [1] (C_3—H), 2·9 complex [4] (—CH_2—CH_2Ar). (Found: C, 71·2; H, 6·45; N, 3·8. $C_{21}H_{23}NO_4$ requires: C, 71·4; H, 6·6; N, 4·0%.)

Methiodide, pale yellow prisms, m.p. 220–222° from $CHCl_3$–EtOH; λ_{max} mμ, (ε) 256 (47,550), 317 (10,850), sh 345 (6795). ν_{max} cm^{-1}, 1650 (>C=N<), 1625, 1600 (>C=C<). (Found: C, 53·4; H, 5·1; N, 3·1. $C_{22}H_{26}NO_4I$ requires: C, 53·3; H, 5·3; N, 2·8%.)

6,7-Dimethoxy-2-methyl-4-(3,4-dimethoxyphenylethyl)1,2-dihydroisoquinoline (**14**). The methiodide (0·2 g) prepared in the previous experiment was carefully dried and pulverized. This material was added in portions to a suspension of LAH (0·2 g) in THF (100 ml). After stirring for 4 hr at room temp the reaction was protected by an atm of N_2 and the excess reagent decomposed by the addition of 33% aqueous sodium potassium tartarate soln. Ether (250 ml) was then added and the combined solvent layer decanted quickly from the solid residue. Water (15 ml) was added to the ethereal layer and the solvents removed under a reduced press of N_2. The solid thus produced was collected and rapidly recrystallized from EtOH, affording pale pink coloured feathery needles (0·11 g), m.p. 89–90°; λ_{max} mμ, (ε) sh 250 (10,233), 285 (4467), 335 (7586). ν_{max} cm^{-1}, 1635, 1600, 1585 (>C=C<). (Found: C, 70·9; H, 7·2; N, 4·2. $C_{21}H_{25}NO_4$ requires: C, 71·0; H, 7·1; N, 3·9%.)

6,7-Dimethoxy-2-methyl-4-(3,4-dimethoxyphenylethyl)1,2,3,4-tetrahydroisoquinoline. 6,7-Dimethoxy-4-(3,4-dimethoxyphenylethyl)isoquinoline methiodide 0·2 g) in EtOH (25 ml) containing water (1 ml) was treated with $NaBH_4$ (0·2 g). After heating for 1 hr on a water-bath the solvent was removed and the tetrahydro-base extracted into ether. Evaporation of the ether gave a colourless gum, which was not obtained crystalline even after chromatography upon alumina, eluting with benzene. TLC showed one spot r.f. 0·7 (silica gel; solvent: 20% diethylamine in $CHCl_3$). NMR ($CDCl_3$) ppm, 6·50 singlet [3] (3 aromatic protons), 6·35 singlet [1] and 6·20 singlet [1] (C_5—H, C_8—H), 3·25 quartet [2] J = 14 c/s, (Ar·CH_2—N<), 2·25 singlet [3] (NCH_3). Methiodide, m.p. 103–105° from MeOH. (Found: C, 52·8; H, 6·35; H, 2·5. $C_{23}H_{32}NO_4I$, CH_3OH requires: C, 52·8; H, 6·65; H, 2·6%.)

3,4-Methylenedioxybenzylaminoacetaldehydedimethylacetal (**21a**). Piperonal (80 g) and aminoacetaldehydedimethylacetal (56 g) in benzene (500 ml) were heated under a Dean Stark head at reflux until the theoretical volume of water had been collected. After removal of the solvent the residue was dissolved in EtOH (500 ml) and hydrogenated at atm press over Adams' catalyst until one mol equiv of H_2 had been taken up. The EtOH was then removed and the residual oil distilled under reduced press to give **21a** as a colourless oily liquid (120 g, 94% yield) b.p. 130–135/1. mm; ν_{max} cm^{-1}, 3330 (NH); NMR (CCl_4) ppm, 6·37 complex [3] (aromatic protons), 5·48 singlet [2] (—O—CH_2—O—), 4·13 triplet [1] (—CH—CH_2—), 3·40 singlet [2] (Ar—CH_2—NH—) 3·07 singlet [6] (2 × OMe), 2·47 doublet [2] (—CH_2—CH—), 1·40 singlet, removed on deuteration [1] (—NH—).

In a similar experiment, **21b** (b.p. 134–135/0·15 mm) was prepared from veratraldehyde in 90% yield.

4-(6,7-Methylenedioxyisoquinolyl)acetic acid hydrochloride (**17a**). 3,4-Methylenedioxybenzylaminoacetaldehydedimethylacetal (20 g) in 6N HCl (400 ml) was stirred at room temp under a N_2 atm for 20 hr. The soln was then warmed on a water-bath for 10 min and glyoxalic acid (8·5 g) in 2N HCl (20 ml) introduced; after heating for a further hr the soln was set aside to cool overnight. The crystalline product was then collected and recrystallized from 2N HCl to give 6,7-methylenedioxyisoquinolyl-4-acetic acid hydrochloride (15·2 g; 68% yield) as yellow needles, m.p. 274° (dec); λ_{max} mμ, (ε) 246 (41,400); ν_{max} cm^{-1}, 1700

(—CO_2H); NMR (CF_3CO_2H) ppm, 8·75 doublet [1] $J = 2$ c/s (C_1—H), 8·05 doublet [1] $J = 2$ c/s (C_3—H), 7·30 singlet [1] (C_8—H), 7·27 singlet [1] (C_5—H), 6·10 singlet [2] (—OCH_2O—), 4·20 singlet [2] (—CH_2—CO_2H). (Found: C, 53·7; H, 3·8; N, 5·4. $C_{12}H_{10}NO_4Cl$ requires: C, 53·8; H, 3·7; N, 5·2%.)

In a similar experiment, **17b** was prepared from 3,4-dimethoxybenzylaminoacetaldehydedimethylacetal in 67% yield as colourless fine needles from 2N HCl. m.p. 228–230°. (Found: C, 55·2; H, 4·90; N, 4·75; Cl, 12·15. $C_{13}H_{14}NO_4Cl$ requires: C, 55·0; H, 5·0; N, 4·9; Cl, 12·5%.)

Trans-α-[4′-(6′,7′-*Methylenedioxy)isoquinolyl*]2-*nitro*-4,5-*methylenedioxycinnamic acid* (**18a**). 6,7-Methylenedioxyisoquinolyl-4-acetic acid hydrochloride (10·0 g), 6-nitropiperonal (7·0 g), AcONa (3·0 g), Ac_2O (150 ml) and $MeNH_2$ (100 ml) were heated under reflux for 4 hr. The resultant hot soln was poured into boiling water (500 ml) and heated with rapid stirring at 100° for a further 10 min. On cooling *trans*-α-[4′-(6′,7′-methylenedioxy)isoquinolyl]2-nitro-4,5-methylenedioxycinnamic acid separated and was collected (11.3 g; 74% yield). This material as the hydrochloride was crystallized from 2N HCl as pale yellow prisms, m.p. > 340° (68%); λ_{max} mμ, (ε) 247 (39,600), 317 (10,000), 331 (9630); ν_{max} cm^{-1}, 2650 (⩾$\overset{+}{N}$H), 1725 (—CO_2H); NMR (CF_3CO_2H) ppm, 8·73 multiplet [1] ($C_{1'}$—H), 8·47 singlet [1] ($C_{3'}$—H), 7·87 multiplet [1] ($C_{3'}$—H), 7·33 singlet [1] (C_6—H, 7·23 singlet [1] ($C_{8'}$—H), 7·13 singlet [1] ($C_{5'}$—H), 6·15 singlet [1] (—CH=C⟨), 6·07 singlet [2] and 5·77 singlet [2] (2 × —OCH_2O—). (Found: C, 53·7; H, 3·2; N, 6·6. $C_{20}H_{13}N_2O_8Cl$ requires: C, 54·0; H, 2·9; N, 6·3%.)

In similar experiments, **18b** was prepared in 64% yield from 6,7-dimethoxyisoquinolyl-4-acetic acid hydrochloride and 2-nitropiperonal as yellow needles, m.p. > 340° from 2N HCl. Compound **18c** was obtained in 62% yield from 4-(6,7-dimethoxy)isoquinolylacetic acid hydrochloride and 2-nitroveratraldehyde.

(Unique NMR spectra and satisfactory analytical figures were obtained for both of these compounds.)

Trans-α-[4′-(6′,7′-*Methylenedioxy)isoquinolyl*]2-*amino*-4,5-*methylenedioxycinnamic acid.* Ferrous sulphate (24 g) in hot water (80 ml) was added to a hot soln of *trans*-α-[4′-(6′,7′-methylenedioxy)isoquinolyl]-2-nitro-4,5-methylenedioxycinnamic acid hydrochloride (4·0 g) in 0·880 ammonia (100 ml) with vigorous stirring. The mixture was heated for 10 min on the water-bath and then filtered and the filtrate neutralized (pH 8) with glacial AcOH. After 24 hr, solid *trans*-α-[4′-(6′7-methylenedioxy)isoquinolyl]-2-amino-4,5-methylenedioxycinnamic acid was collected (2·2 g, 60%). Recrystallization of this material or its hydrochloride salt was not achieved; ν_{max} cm^{-1}, 3430, 3330 (—NH_2), 1675 (—CO_2H); NMR (CF_3CO_2H) ppm, 8·37 multiplet [1] ($C_{1'}$—H), 8·13 multiplet [1] ($C_{3'}$—H), 7·27 singlet [1] ($C_{8'}$—H), 7·17 broad singlet [2] (C_3—H and C_5—H), 6·95 singlet [1] (C_6—H), 6·72 singlet [1] (—CH=C⟨), 5·97 singlet [2] and 5·77 singlet [2] (2 × —OCH_2O—).

In analogous experiments the reductions of *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-nitro-4,5-methylenedioxycinnamic acid and *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-nitro-4,5-dimethoxycinnamic acid hydrochloride were achieved. The yields of crude amine were 71 and 65% respectively, these amorphous solids were exceptionally difficult to recrystallize and were used unpurified in the subsequent reactions.

2,3,8,9-*Bismethylenedioxy-benzo*[*c*]*phenanthridine* (**5b**). *trans*-α-[4′-(6′,7′-Methylenedioxy)isoquinolyl]-2-amino-4,5-methylenedioxycinnamic acid (2·0 g) in 2N HCl (120 ml) was treated with a soln of $NaNO_2$ (0·55 g) in water (40 ml). Excess HNO_2 was decomposed by the addition of urea and Cu powder (2·0 g) then added. After stirring at room temp for 5 hr the mixture was filtered. The solid product was dried and then suspended in quinoline (10 ml) and heated at 230° for 20 min, water was then added and most of the quinoline was removed by steam distillation. The solid residue from the steam distillation was continuously extracted with chloroform for 24 hr, the extracts were then combined and evaporated to give the crude benzol[c]phenanthridine. This material was sublimed at 250°/0·05 mm press to yield 0·4 g of the pure benzo[c]phenanthridine which was finally recrystallized from pyridine as cream coloured needles, m.p. 328° dec (lit.[3] 325° dec), yield 18%; λ_{max} mμ, (ε) 230 (25,120), 274 (60,260) 352 (4460, 369 (3020). ν_{max} cm^{-1}, 1635 (⟩C=N—); NMR (CF_3CO_2H) ppm, 8·83 multiplet [1] (C_6—H), 7·97 doublet [1] $J = 10$ c/s (C_{11}—H), 7·75 singlet [1] (C_7—H), 7·70 doublet [1] $J = 10$ c/s. (C_{12}—H) 7·62 singlet [1] (C_{10}—H), 7·37 singlet [1] (C_4—H), 7·08 singlet [1] (C_1—H), 6·22 singlet [2] and 6·05 singlet [2] (2 × —OCH_2O—). (Found: C, 71·9; H, 3·4; N, 4·6. Calc. for $C_{19}H_{11}O_4N$: C, 71·9; H, 3·5; N, 4·4%.)

2,3,8,9-*Tetramethoxybenzo*[*c*]*phenanthridine* (**5a**). In an exactly analogous experiment *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-amino-4,5-dimethoxycinnamic acid was converted into 2,3,8,9-tetramethoxybenzo[c]phenanthridine. Sublimation of the crude product at 220°/0·1 mm and recrystallization

from pyridine–EtOH gave colourless plates m.p. 305–307° (lit.[5] 302–304). (Found: C, 72·4; N, 5·5; N, 4·0. Calc. for $C_{21}H_{19}NO_4$: C, 72·2; N, 5·5; N, 4·0%.)

2,3-*Methylenedioxy*-8,9-*dimethoxybenzo*[*c*]*phenanthridine* (**5c**). *trans*-α-[4'-(6',7'-Dimethoxy)isoquinolyl] 2-amino-4,5-methlenedioxycinnamic acid gave a 15% yield of the corresponding **5c** when diazotized and reacted under the conditions described above. Recrystallization from pyridine–EtOH gave colourless needles, m.p. 277–279° (lit.[4] 277–287°); λ_{max} mμ, (ε) 230 (36,300), 275 (63,100), 315 (24,000), 370 (2100). (Found: C, 72·1; H, 4·6; H, 4·7. Calc. for $C_{20}H_{15}NO_4$: C, 72·1; H, 4·5; H, 4·2%.)

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1,2-DIHYDROISOQUINOLINES - REARRANGEMENT II

(Tetrahedron, 1968, 24, 6695)

Tetrahedron. Vol. 24, pp. 6695 to 6702. Pergamon Press 1968. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—VIII[1]

REARRANGEMENT—II

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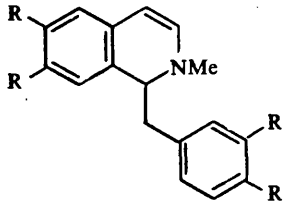
Abstract—The acid promoted rearrangement of 1-allyl-2-methyl-1,2-dihydroisoquinoline to the corresponding 3-aliyl-2-methyl-3,4-dihydroisoquinoline salt has been observed and the behaviour of 1-benzyl-2-methyl-1,2-dihydroisoquinoline and 2-methyl-1,2-dihydropapaverine towards various conditions of acid concentration and temperature has been studied.

KNABE and Kubitz reported[2] in 1963 that when 2-methyl-1,2-dihydropapaverine (**1**; R = R^1 = OMe) was treated with dilute aqueous acid at 100° for a few minutes rearrangement occurred to give the 3-benzyl-3,4-dihydroisoquinolinium salt (**2**, R = R^1 = OMe). The mechanism of the rearrangement was shown[3] to involve a migration of the benzyl group from position-1 to position-3 of the isoquinoline system and it was thought initially that the reaction was intramolecular in nature, involving a species such as **3**, formed by the C_4-protonation of the 1,2-dihydroisoquinoline.[2,3]



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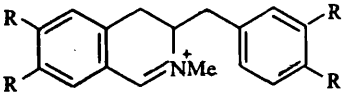
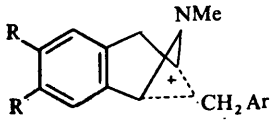


2

When, however, a mixture of **1** (R = R^1 = OMe) and (R = R^1 = OEt) was treated with dilute HCl under the conditions of the rearrangement four 3-benzyl-3,4-dihydroisoquinolinium salts were formed,[4] indicating that cross migration had occurred, and on this evidence Knabe now favours an intermolecular course for the rearrangement. Knabe and Ruppenthal[5] have further shown that rearrangement



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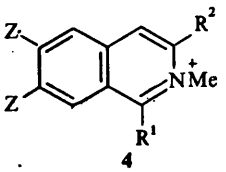
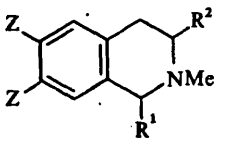


4

followed by disproportionation into **4** (Z = OMe, R_1 = H, R_2 = *p*-bromobenzyl) and **5** (Z = OMe, R^1 = H, R^2 = *p*-bromobenzyl) occurs when 1-(4-bromobenzyl) 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline is treated with dilute mineral acid, but that disproportionation without rearrangement to give **4** (Z = OMe,



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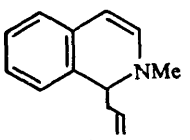


6

R_1 = Alkyl, R_2 = H) and 5 (Z = OMe, R^1, = alkyl, R^2 = H) is observed when the 1-substituent is methyl, n-butyl and β-phenethyl. A similar result is obtained when the 1-substituent is phenyl.[5,6]

We have now found that when 1-allyl-2-methyl-1,2-dihydroisoquinoline (6), prepared by the addition of allyl magnesium bromide to isoquinoline methiodide, is heated with 2N HCl, under the conditions employed for benzyl migration, a quaternary salt, isolated in 60% yield as the pseudocyanide, was formed. A signal at 4·7 ppm in the NMR spectrum of this material (Fig. 1) is assigned to a hydrogen atom

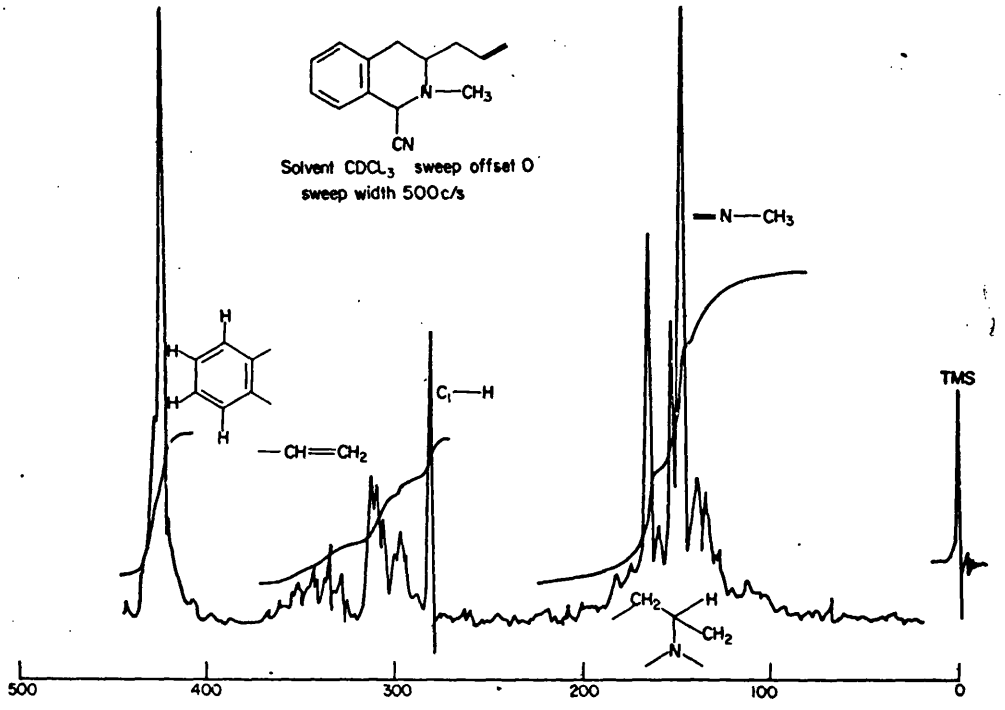


FIG. 1

at C_1 of the isoquinoline ring and the three proton complex centred at about 5·3 ppm indicates the presence of the allyl group. Structure 7 for the quaternary salt, which is reformed from the pseudocyanide by treatment with HCl, was established by showing that the product obtained from it by catalytic hydrogenation is identical (superimposable IR and NMR spectra and mixed m.p. of the derived methiodides) with a sample of 2-methyl-3-n-propyl-1,2,3,4-tetrahydroisoquinoline prepared in a standard manner from the amine 8. The authenticity of the parent 1,2-dihydroisoquinoline (6) was confirmed by its characteristic UV and NMR (Fig. 2) spectra

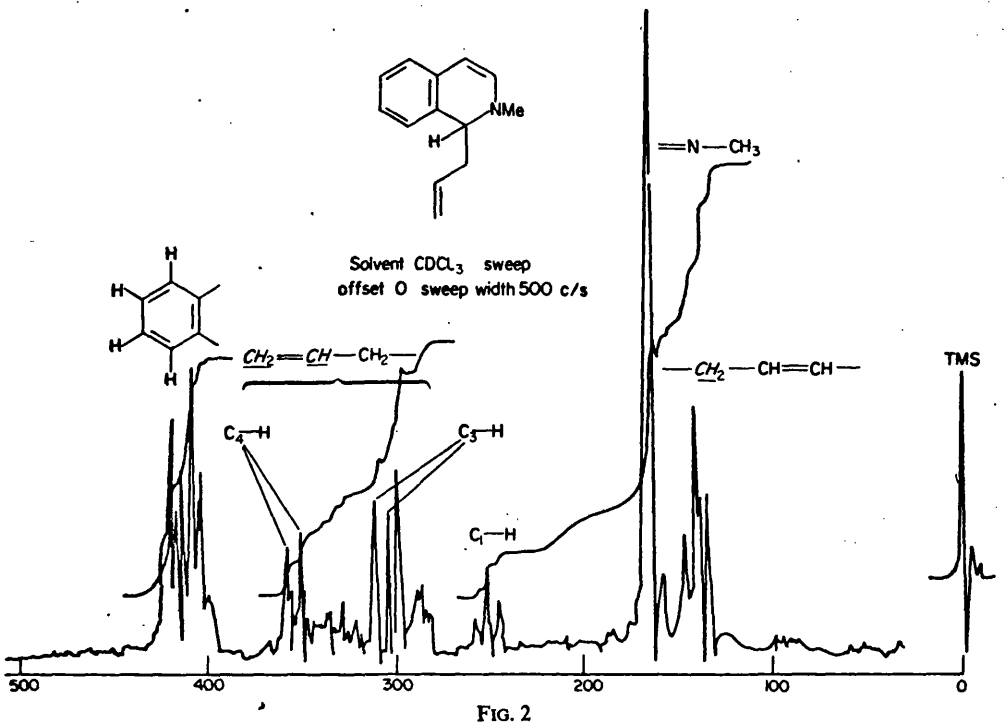
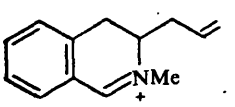


FIG. 2



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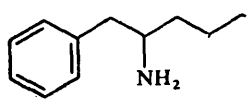

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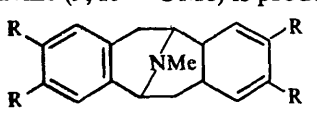
and by the fact that catalytic reduction gave a compound identical (superimposable IR and NMR spectra and mixed m.p. of methiodides) with a synthetic specimen of 1-n-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline.

Whilst the mild conditions of acid treatment described above brings about the rearrangement of **1** into **2**, more severe conditions have been known for some time to cause cyclization to compounds of the type **9**; for example when **1** (R = R^1 = OMe) is heated at 120° with a mixture of orthophosphoric and formic acids for 5 hr, N-methylpavine (**9**, R = OMe) is produced in 72% yield.[7]



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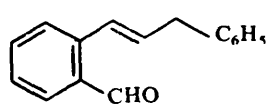

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It was of interest to us to ascertain whether a threshold condition exists between the rearrangement and cyclization reactions of a 1-benzyl-1,2-dihydroisoquinoline and we have examined the behaviour of the parent compound **1** (R = R^1 = H) under various conditions of acid treatment. It has already been shown[8] that when **1** (R = R^1 = H) is heated at 155° for 48 hr with conc H_3PO_4 in a molar ratio of base to acid of 1:48, the pavine-type structure **9** (R = H) is formed in 11% yield.

This structure was proved in a series of degradations. An iodide salt, $C_{17}H_{18}N$ I, m.p. 165–166° was also isolated (9% yield) from the reaction mixture, but a structural assignment was not made.

When **1** (R = R^1 = H) was treated with 2N H_2SO_4 or 2N H_3PO_4 (molar ratio 1:1) at 100° for 2 hr, a new quaternary salt was formed and isolated in 75% yield, iodide m.p. 166–168°. The compound was further characterized by reduction with $NaBH_4$ to the 1,2,3,4-tetrahydroisoquinoline and conversion to the methiodide and the picrate. The UV spectrum of the reaction product was characteristic of a 3,4-dihydroisoquinolinium salt, and the NMR spectrum is consistent with the structure of 2-methyl-3-benzyl-3,4-dihydroisoquinolinium iodide (**2**, R = R^1 = H).

Degradation of the quaternary salt with methyl sulphate and alkali yielded a nitrogen-free oil whose NMR spectrum (Fig. 3) confirms the presence of an aldehyde

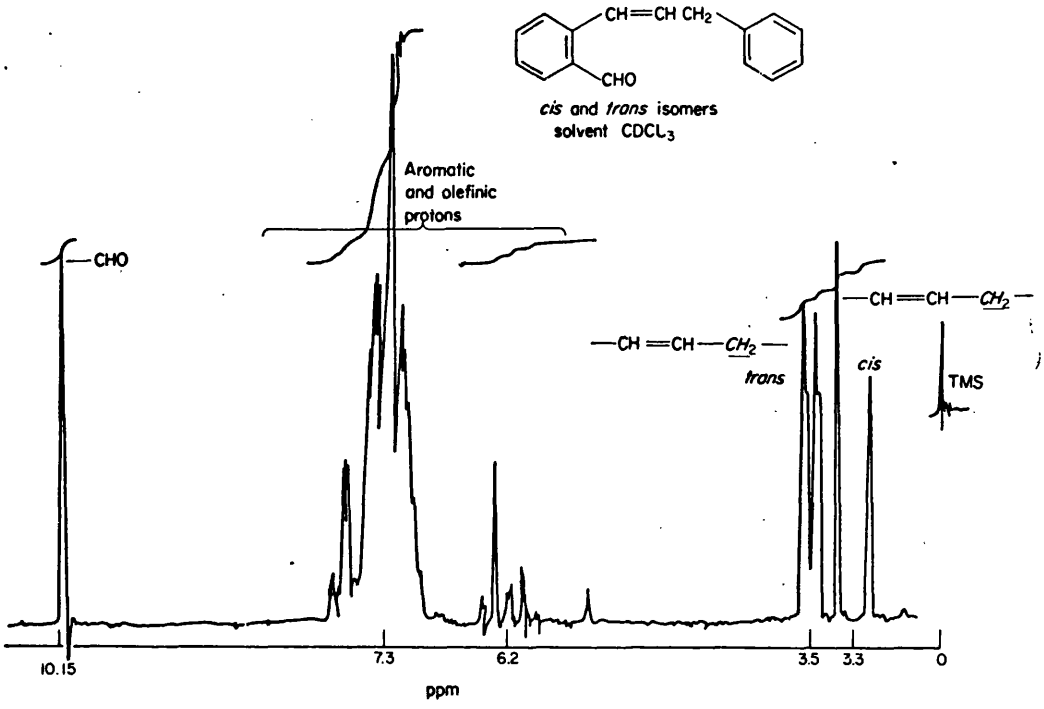

FIG. 3

group (a one proton singlet at 10·15 ppm). The complexity of the signals at 3·3, 3·5 and 6·2 ppm suggests that the compound is probably a mixture of the two geometrically isomeric *o*-formyl styrenes (**10**). Chromatography of the oil on silica gel plates confirms the presence of two closely related compounds. The isolation of an aldehyde in this degradation confirms that rearrangement of **1** (R = R^1 = H) has occurred since a 1-substituted-3,4-dihydroisoquinolinium salt would yield a ketone under the degradative conditions employed.[9] The iodide, m.p. 165–166° obtained by Wittig *et al.*[8] was shown, as expected, to be identical with **2** (R = R^1 = H).

With a molar ratio of **1** (R = R^1 = H) to acid of 1:2, the yield of the cyclized product **9** (R = R^1 = H) was raised to 19%, but in this experiment some starting material (4%) was isolated together with a mixture (4%) of two further bases, which

were shown to be 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**, Z = H, $R^1 = CH_2C_6H_5$, R^2 = H) and 3-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**, Z = H, R^1 = H, $R^2 = -CH_2C_6H_5$), by chromatographic comparison with authentic specimens, and formed presumably by disproportionation. The corresponding fully aromatic compounds **4** (Z = R^2 = H, $R^1 = -CH_2C_6H_5$ and Z = R^1 = H, $R^2 = -CH_2C_6H_5$) were shown to be present in the mixture of quaternary salts also produced by the reaction.

A 57% yield of the rearranged compound **2** (R = R^1 = H) was additionally obtained.

Altogether five sets of conditions of acid treatment of **1** (R = R^1 = H) were studied (Experimental) and in each case the rearrangement was the major reaction pathway, but whereas under mild conditions of acid treatment the most important secondary reaction seems to be disporportionation of the starting material, at high temperature cyclization to **9** (R = R^1 = H) becomes more important.

An attempt was made to carry out a parallel study with 2-methyl-1,2-dihydropapaverine, and to examine the products by reduction and GLC analysis. Unfortunately the retention times of N-methylpavine (**9**, R = OMe) and the tetrahydroisoquinoline (**5**, Z = OMe, R^1 = H, R^2 = 3,4-dimethoxybenzyl) proved to be so similar, under the conditions which we could employ, that satisfactory resolution of the peaks due to these two components was not achieved. The indications are however that rearrangement persists under vigorous conditions and that N-methylpavine formation diminishes in importance as the concentration of acid and the temperature of the reaction are lowered.

EXPERIMENTAL

NMR spectra were recorded upon a Varian A-60 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. IR spectra were determined as Nujol mulls upon a Perkin–Elmer 237 instrument and UV spectra were recorded as ethanolic solns upon a Perkin–Elmer 137 spectrometer. All m.ps are uncorrected.

Acid treatment of 1-*benzyl*-2-*methyl*-1,2-*dihydroisoquinoline* (*General procedure, see Table* 1). After heating the 1,2-dihydroisoquinoline (5 g) with acid, under N_2, the reaction mixture was poured into water (1 l.) and the pH adjusted to 8. Basic components were extracted into ether and separated by thin film chromatography upon SiO_2, developing the plates with 1:9 mixture of EtOAc:petrol (60–80). When viewed under UV light three main bands were observed; R_f, 0·2–0·3, 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline and 3-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (which were not resolved), R_f, 0·38–0·42, cyclized material (**9**, R = H) and R_f 0·65–0·67, 1-benzyl-2-methyl-1,2-dihydroisoquinoline. The aqueous $NaHCO_3$ soln, after the removal of basic compounds, was treated with KCN and again ether extracted; removal of the solvent gave the pseudocyanide of the rearranged compound **2** (R = R^1 = H). Addition of $HClO_4$ to the aqueous phase caused the precipitation of a mixture of the isoquinolinium salts (**4**, Z = R^2 = H, $R^1 = CH_2C_6H_5$ and Z = R^1 = H, $R^2 = CH_2C_6H_5$).

Characterization of the rearrangement material (**2**, R = R^1 = H). The pseudocyanide from the above separation was dissolved in 2N HCl (25 ml) and heated for 15 min on a water-bath, KI was then added and the yellow iodide salt collected, and recrystallized from acetone as needles m.p. 168–169°. ν^{max} cm^{-1}, 1663 (>C...N<). λ_{max} (ε) mμ, 217 (26,920), 285 (10,720).

NMR ($CDCl_3$) ppm, 9·95 singlet [1] (C_1H), ~7·8 complex [4] (aromatic protons), 7·3 singlet [5] (aromatic protons of benzyl group), ~4·55 complex [1] (C_3—H), 3·9 singlet [3] (>$\overset{+}{N}$—CH_3), ~3·0 complex [4] (C_4 protons plus —CH_2—Ph). [Found: C, 56·1; H, 5·3; N, 3·9. $C_{17}H_{18}NI$ requires: C, 56·2; H, 5·0; N, 3·9%]. Reduction of this compound with $NaBH_4$ in aqueous EtOH gave **5** (Z = R^1 = H, $R^2 = CH_2C_6H_5$) as a pale yellow oil. TLC on alumina using EtOAc and 60–80° pet ether (1:9) showed, under

Table 1

Acid	Ratio Base:Acid	Temp. °C	Time hr.	% Rearrangement product 2, R = R^1 = H)	% Cyclized compound (9, R = H)	% 1- and 3-Benzyl -2-methyl tetra-hydroisoquinolines (5, Z = R^2 = H, R^1 = —CH_2—C_6H_5 and 5, 2 = R^1 = H, R^2 = —$CH_2C_6H_5$)	% 1- and 3-Benzyl -2-methylisoquinolinium salts. (4, Z = R^2 = H, R^1 = —$CH_2C_6H_5$ and 4, Z = R^1 = H, R^2 = —$CH_2C_6H_5$	% Unchanged starting material (1, R = R^1 = H)
90% H_3PO_4	1:43	155	48	11*	9	—	—	—
90% H_3PO_4	1:22	155	48	57	19	4	5	4
90% H_3PO_4	1:2	155	48	59	1	8	8	21
90% H_3PO_4	1:1	100	2	75	0	—	—	12
2N HCl	1:2	100	2	75				

* During this experiment much charring occurred, rendering the work-up procedure difficult.

UV, one spot R_f 0·45. 1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline under the same conditions has R_f 0·55. The methiodide was prepared as colourless needles m.p. 197–198° from aqueous MeOH, mixed m.p. with 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline methiodide (m.p. 249–253°; lit.,[8] 241–243°) depressed. [Found: C, 57·1; H, 5·7; N, 3·8. $C_{18}H_{22}NI$ requires: C, 57·0; H, 5·9; N, 3·7%].

Degradation of compound **2** (R = R¹ = H) *with alkaline* Me_2SO_4. The pseudocyanide was heated with 2N HCl (20 ml) on a water-bath for 15 min and then made strongly alkaline with 15% NaOH aq (10 ml). Me_2SO_4 (6 ml) was then added, together with more NaOH aq (10 ml) and the mixture was heated under reflux for 3 hr. This gave an emulsion, which was extracted with ether (2 × 25 ml); removal of the ether afforded a brown oil, which showed bands at 2870, 2760 and 1695 cm^{-1} in the IR spectrum due to an aldehyde group and a band at 1650 cm^{-1} consistent with an olefinic double bond. TLC on SiO_2 showed the presence of two compounds and the NMR spectrum (in $CDCl_3$) indicated an equimolar mixture of *cis* and *trans* isomers of o-formylbenzylstyrene (**10**) the aldehydic proton signals falling together at 10·15 ppm.

Characterization of cyclized material (**9**, R = H). The band R_f 0·38–0·42 on the preparative plate was removed and extracted several times with $CHCl_3$; evaporation of the solvent yielded 2-methyl-1-methylene-3-o-benzylene-1,2,3,4-tetrahydroisoquinoline as a pale brown oil, from which the methiodide was prepared. This compound was recrystallized as colourless needles from MeOH had m.p. 306° (lit.,[8] 305–306°). [Found: C, 57·2; H, 5·2; N, 3·7. Calc. for $C_{18}H_{20}NI$: C, 57·3; H, 5·3; N, 3·7%].

1-*Allyl*-2-*methyl*-1,2-*dihydroisoquinoline* (**6**). Allylmagnesium bromide (1 mole) in ether was added in the course of 2 hr to a suspension of isoquinoline methiodide (1 mole) in ether (400 ml), protected by an atmosphere of N_2. After stirring overnight, at room temp, water (200 ml) was added and when the initial violent reaction had subsided, the ether layer was separated and rapidly extracted with ice-cold 2N HCl. The combined acid extracts were basified with NH_4OH and re-extracted with ether; after combination and drying the ether extracts were evaporated to give 1-allyl-2-methyl-1,2-dihydroisoquinoline as a pale yellow oil (14% yield); ν_{max} cm^{-1}, 1625, 1620. λ_{max} mμ, 240 (Sh), 339. NMR ($CDCl_3$) ppm, ~6·7 complex [4] (aromatic protons on isoquinoline ring), 6·05 doublet [1] J = 9 c/s (C_4—H), 6·1–4·7 complex [2] (CH_2=CH—CH_2—) 5·1 doublet [1] J = 9 c/s (C_3—H), 4·15 triplet [1] J = 6 c/s (C_1—H), 2·9 singlet [3] (>N—CH_3). 2·3 complex [2] (—CH_2—CH=CH_2).

1-*Propyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**5**, Z = R² = H, R¹ = *propyl*). Catalytic hydrogenation of **6** gave **5** (Z = R² = H, R¹ = propyl) as a colourless oil, characterized as the methiodide, colourless needles m.p. 130–132° from acetone. [Found: C, 50·3; H, 7·0; N, 4·3. $C_{14}H_{22}NI$ requires: C, 50·8; H, 7·0; N, 4·2%].

The free base from the above reaction was shown to be identical with a sample of 1-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline prepared from 1-propyl-2-methyl-3,4-dihydroisoquinolinium iodide m.p. 134–136° (identical NMR, UV and IR spectra). (lit.,[10] 132–134°) by sodium borohydride reduction. The methiodide of the tetrahydro-base prepared in this way caused no depression in m.p. when mixed with the methiodide (m.p. 130–132°) described above.

Acid treatment of 1-*allyl*-2-*methyl*-1,2-*dihydroisoquinoline*. The 1,2-dihydroisoquinoline (3 g) in 2N H_2SO_4 (10 ml) was heated on a water-bath for 6 hr and allowed to stand at room temp overnight. After the addition of water (100 ml) the soln was washed with ether, basified with $NaHCO_3$ and extracted with ether. Evaporation of the combined ether extracts gave unchanged starting material (1·4 g) and addition of KCN to the aqueous soln followed by ether extraction afforded a pale yellow oil (1·3 g) NMR ($CDCl_3$) ppm 6·85 complex [4] (aromatic protons), 6·2–4·8 complex [3] (CH_2=CH—CH_2—), 4·7 singlet [1] (C_1—H), 3·1–1·7 complex [5] (Ar.CH_2—CH<(N= / CH_2—)) 2·4 singlet [3] (=N—CH_3) 3-allyl-2-methyl-3,4-dihydroisoquinolinium chloride. This compound, an unstable red oil, was hydrogenated at 3 atm press over Adam's catalyst, yielding, after basification, the corresponding tetrahydroisoquinoline as a pale yellow oil (1·0 g), characterized as the methiodide m.p. 173–175° colourless prisms from acetone. [Found: C, 50·4; H, 6·4; N, 4·4; I, 38·9. $C_{14}H_{22}NI$ requires: C, 50·8; H, 7·0; N, 4·2; I, 38·3%].

3-*Propyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**5**, Z = R¹ = H, R² = *propyl*. 1-Phenyl-2-pentanone (12·8 g)[12] was heated with ammonium formate (50 g), 98% formic acid (15 ml) and formamide (15 ml) for 3½ hr at 185°. After cooling, the reaction mixture was poured onto water (400 ml) and extracted with ether (2 × 100 ml). The combined ether extracts were washed with NH_4OH and then dried and evaporated to yield the intermediate amide, which was not purified but heated directly with 90% H_3PO_4 (50 ml)

and P_2O_5 (90 g) at 200–210° for 3 hr. After standing at room temp overnight the mixture was poured onto crushed ice and extracted with benzene, the aqueous phase was then separated, basified with Na_2CO_3 aq and again extracted with benzene. This time the combined extracts were evaporated to give 3-propyl-3,4-dihydroisoquinoline (6·7 g) as a colourless oil, b.p. 4 mm 124–126° (lit.,[11] b.p. 4 mm 120–121°). The methiodide of this compound was prepared and reduced with $NaBH_4$ in aqueous MeOH to yield 3-propyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (4·9 g) as a yellow oil, characterized as the methiodide, m.p. 173–176°, colourless needles from acetone. [Found: C, 50·5; H, 6·9; N, 4·1. $C_{14}H_{22}NI$. Requires: C, 50·8; H, 7·0; N, 4·2%].

A direct comparison of the free base from the above reaction and the tetrahydroisoquinoline from the acid treatment of 1-allyl-2-methyl-1,2-dihydroisoquinoline showed them to be identical (NMR and IR spectra), a conclusion supported by mixed m.p.s of the corresponding methiodides.

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SOME DIBENZO[a,h]QUINOLIZINE DERIVATIVES

(Tetrahedron Letters, 1968, 2671)

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SOME DIBENZO[a,h]QUINOLIZINE DERIVATIVES

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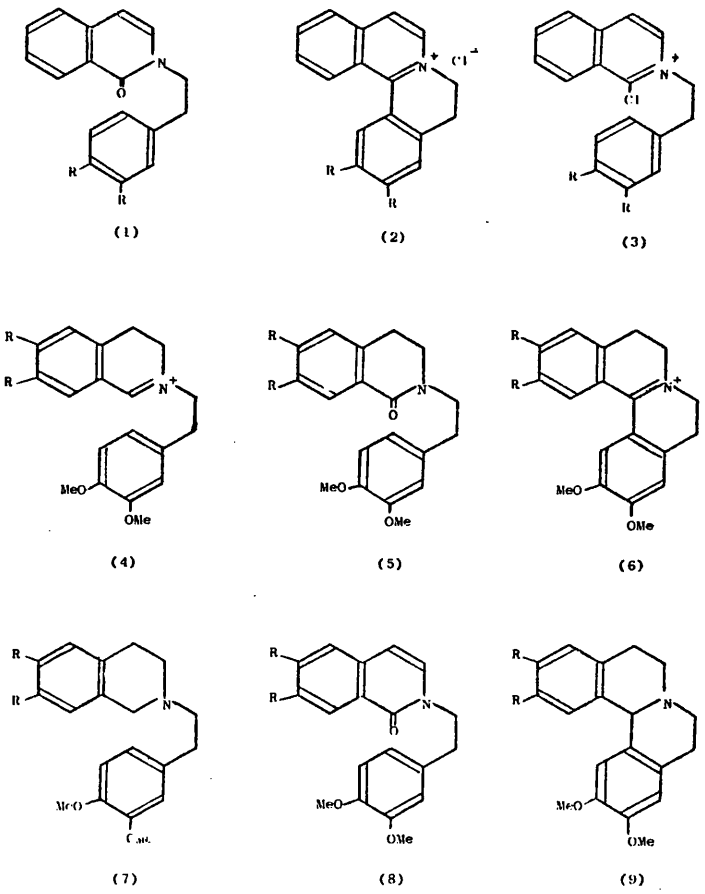
Akahoshi has claimed[1] that when the isocarbostyrils (1a) and (1b) are treated with $POCl_3$, cyclisation to the dibenzo[a,h]quinolizine derivatives (2a) and (2b) respectively occurs, but we have recently shown[2] that the products are actually the 1-chloroisoquinolinium salts (3a) and (3b) respectively. It has also been reported[3] that oxidation of (4b) yields the dihydroisocarbostyril (5b), which can be cyclised by $POCl_3$ to (6b), but we were able to show[2] that the dihydroisocarbostyril (5b) is not formed under the conditions described, and that the "cyclisation" product is simply the tetrahydroisoquinoline (7b).

We have now found that the dihydroisocarbostyril (5b) can be prepared[4] by the hydrogenation of the corresponding isocarbostyril (8b) and that when it is reacted with $POCl_3$, cyclisation does occur to yield (6b). The structure (6b) follows from the fact that only FOUR aromatic protons are discernible in its NMR spectrum and also its dihydroderivative (9b) is different from (7b). The whole sequence of reactions has also been performed on (8a) with the eventual formation of the dibenzo[a,h]quinolizine derivative (6a).

It was with considerable interest that we read the recent paper[5] in which it was claimed that during the formation of the 3,4-dihydroisoquinolinium salts (4a) and (4b) from the 3,4-dihydroisoquinolines and β-[3,4-dimethoxy]phenethyl bromide, small amounts of (9a) and (9b), respectively, were formed, particularly when the structural proof rested upon a comparison of the basic material with that obtained by Sugasawa and Kakemi[3] as described above. Repetition of the reactions as described[5] quickly confirmed our suspicions that the basic products are not

(a) series: R=H
(b) series: R=OMe



the dibenzo[a,h]quinolizine derivatives (9a) and (9b), but the tetrahydroisoquinolines (7a) and (7b) respectively, formed, presumably, by disproportionation of the dihydroisoquinolines followed by alkylation.

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THE SYNTHESIS OF SANGUINARINE

(Tetrahedron Letters, 1968, 3933)

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THE SYNTHESIS OF SANGUINARINE

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The elucidation of the structure of the benzo[c]phenanthridine alkaloid chelidonine (1) has been well summarised by Manske[1] and by Crawford[2]; in the course of the work chelidonine was transformed oxidatively into the N-methylbenzo[c]phenanthridinium salt (2), which was shown to be identical with the alkaloid sanguinarine.

We wish now to report the first synthesis of this latter alkaloid along the lines that we have established[3] for the preparation of other compounds of this group. The chart summarises the essential steps[4] involved. The final product, obtained in 4% overall yield from 2-3-methylenedioxybenzaldehyde, was found to be identical (superimposable UV and IR spectra and mixed m.p.) with an authentic sample[5] of sanguinarine chloride.

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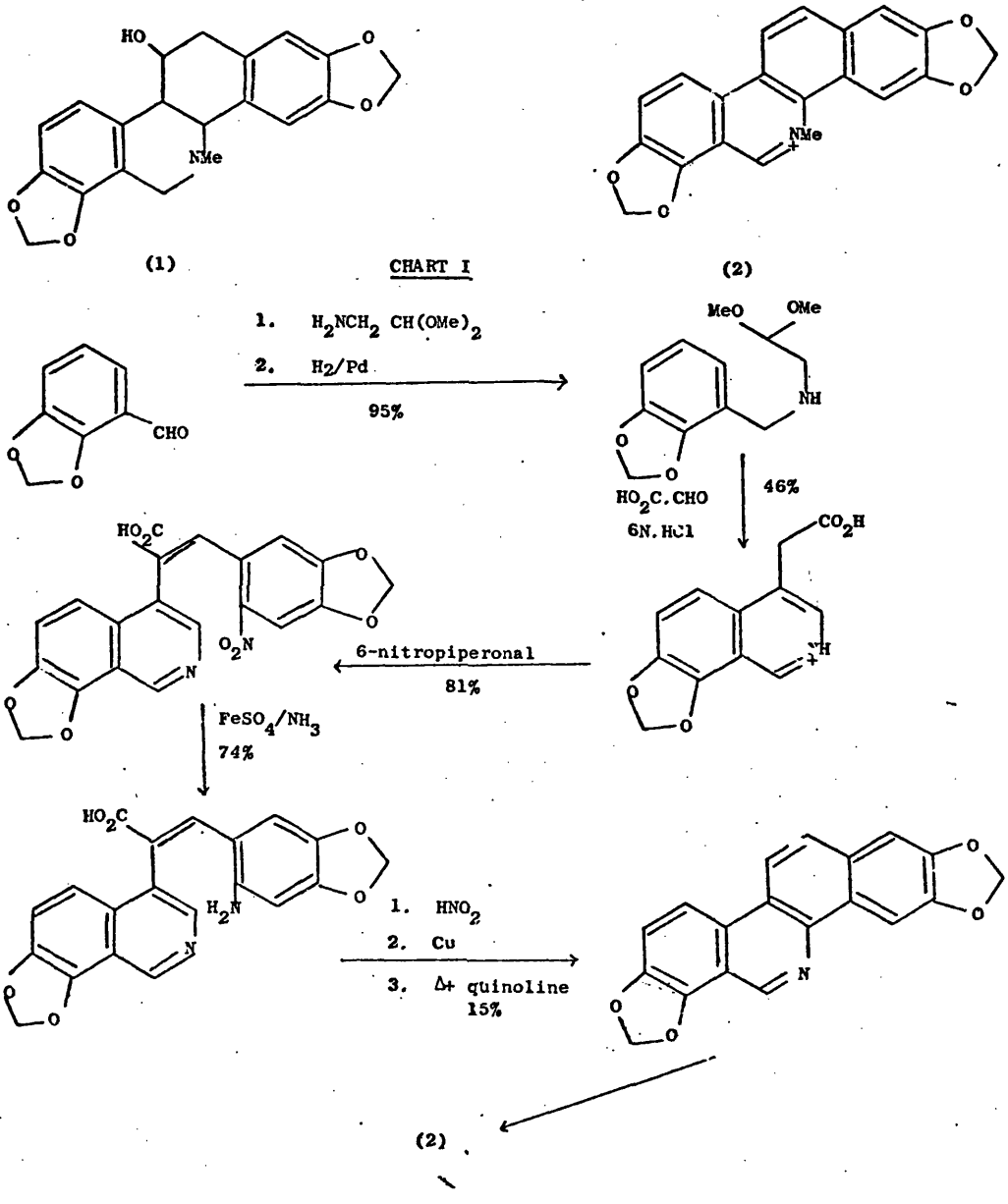
3. S.F. Dyke, M. Sainsbury and B.J. Moon, Tetrahedron, 24, 1467 (1968).
4. Satisfactory Analyses and Spectral Data were secured for all compounds described.
5. It is a pleasure to thank Dr. J. Slavik, Institute of Medicinal Chemistry, Purkyne University, Czechoslovakia for a sample of sanguinarine chloride.


HO
NMe
(1)
(2)
CHART I
1. $H_2NCH_2CH(OMe)_2$
2. H_2/Pd
95%
CHO
MeO
OMe
NH
$HO_2C.CHO$
6N.HCl
46%
CO_2H
HO_2C
O_2N
6-nitropiperonal
81%
$FeSO_4/NH_3$
74%
H_2N
1. HNO_2
2. Cu
3. Δ+ quinoline
15%
(2)

THE INFLUENCE OF ACIDS UPON 4-BENZYL-1,2-DIHYDROISOQUINOLINE DERIVATIVES

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The Influence of Acids on 4-Benzyl-1,2-dihydroisoquinoline Derivatives

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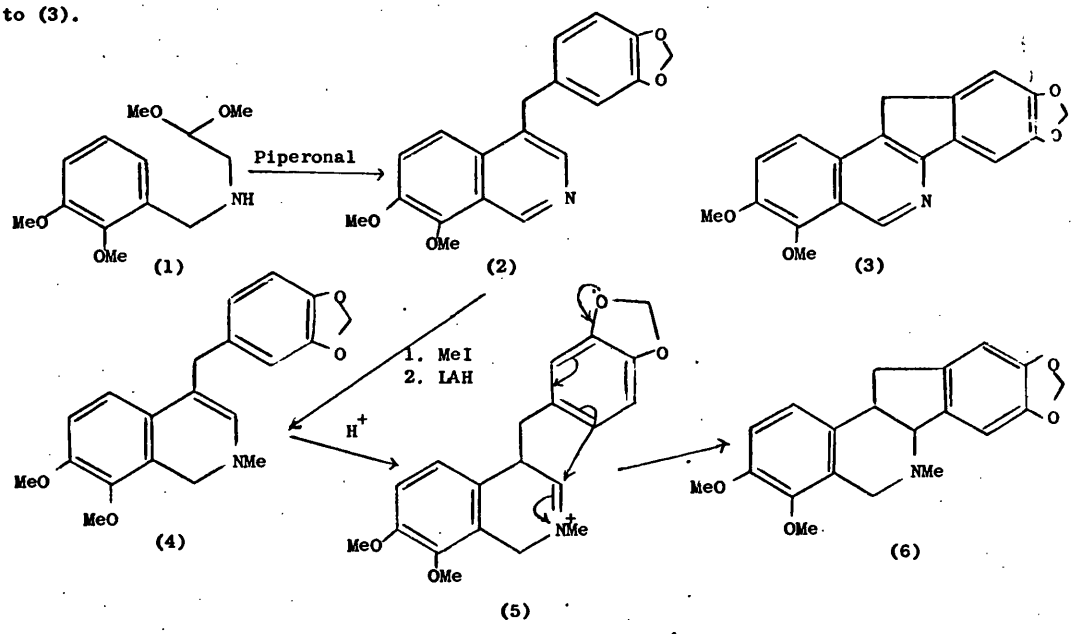
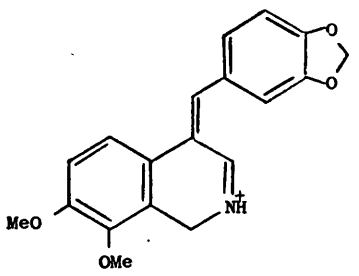
It has been shown[1,2] that aromatic aldehydes react with benzylaminoacetaldehyde dialkyl acetals, for example (1), in the presence of acids, to form 4-benzylisoquinoline derivatives. Recently Gensler et al[3] have reported the isolation of a small amount of the indenoisoquinoline (3) as well as (2), hydrochloride m.p. 100-102°, from the interaction of (1) with piperonal. They further claim that the 1,2-dihydroisoquinoline (4) obtained by reducing the methiodide of (3) with LAH cyclises when treated with an acetic acid-hydrochloric acid mixture to form (6) via the imminium ion (5). The structure for this product (an oil) was supported by the dehydrogenation of (6) with iodine to form a quaternary salt said to be identical with the methiodide of (3), m.p. 243-245°.

Our interest in indenoisoquinoline derivatives stems from our study[4] of some reactions of cryptopine and we have also reacted (1) with piperonal and have obtained (3) as described by Gensler et al, but the major product, hydrochloride m.p. 100-102° was found to be (7), which is easily isomerised to (2) when attempts are made to release the base from its hydrochloride. In our hands treatment of the 1,2-dihydroisoquinoline (4) with acetic-hydrochloric acid mixture as described by the previous workers, or with perchloric acid, led not to ring-closure but to disproportionation. The products of the reaction were conclusively shown to be the metho-salt of (2) and the 4-benzyl-1,2,3,4-tetrahydroisoquinoline (8). Some isomerisation of (4) to (10) was also observed. A similar disproportionation was observed in our previous attempts[2b] to cyclise (9). It is possible for ring-closure of (8) to occur during the dehydrogenation with iodine, so an authentic specimen of (6), m.p. 155-156° was prepared by reducing the methiodide of (3) m.p. 253-254° with $NaBH_4$. We were not surprised to find that quaternisation of (3) with methyl iodide was unsatisfactory; the reaction of the base with dimethyl sulphate, followed by KI, was a superior method. The product (6) was found not to be identical with the base produced by acid treatment of (4).

It is our contention that protonation of 4-substituted-1,2-dihydroisoquinolines such as (4) to form the imminium ion (5) necessary for cyclisation to (6) is inhibited by the C_4-substituent. Consistent with this view is our observation that reduction of 4-benzyl-isoquinolinium salts with $NaBH_4$ leads to the 1,2-dihydroisoquinoline and not to the expected 1,2,3,4-tetrahydroisoquinoline derivatives. The generally accepted mechanism[5] for this latter reduction (11) ⟶ (14) involves an imminium ion (13) as an intermediate. A different situation exists when an electron-donating group is attached to C_3 of a 4-substituted-1,2-dihydroisoquinoline; thus epicryptopirubin chloride (15) can[4] be protonated, and reduced by $NaBH_4$ and the methiodide of (3) behaves similarly. The formation of the indenoisoquinoline (3) during the reaction of (1) with piperonal is readily rationalised since the required imminium ion (18) is produced during the electrophilic attack of piperonal at C_4 of the 1,2-dihydroisoquinoline (16), formed from (1), and NOT by protonation of a 4-benzyl-1,2-dihydroisoquinoline. The product (18) may be precipitated as the hydrochloride from the reaction mixture or may cyclise to (19) which can be aerially oxidised to (3), or the cyclisation may occur in the intermediate (17) to form (20) which may then undergo dehydration to (19). A precedent exists[4] for the ready oxidation of (19) to (3).





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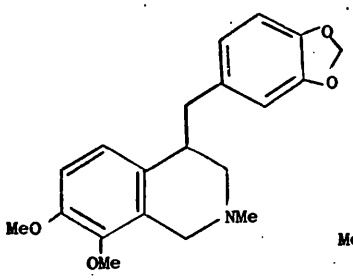

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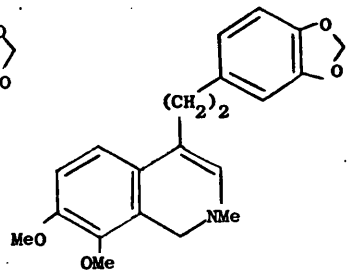

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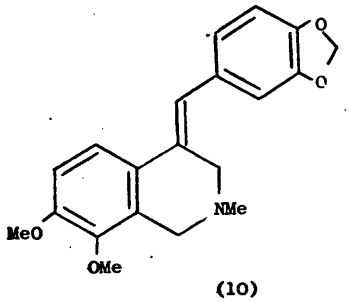

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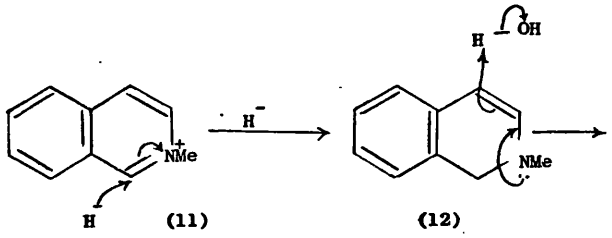

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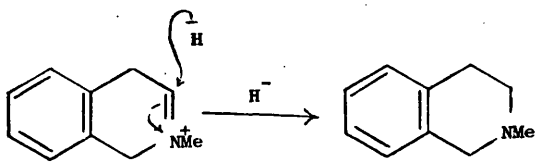

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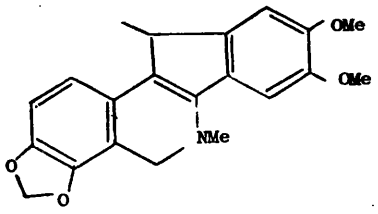

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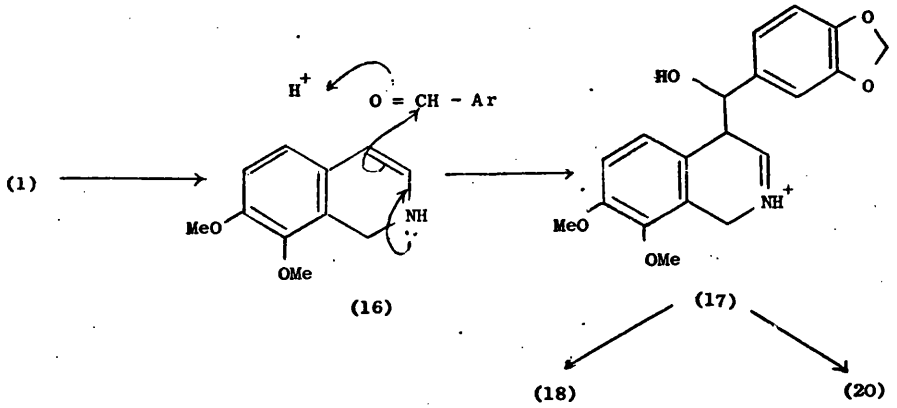
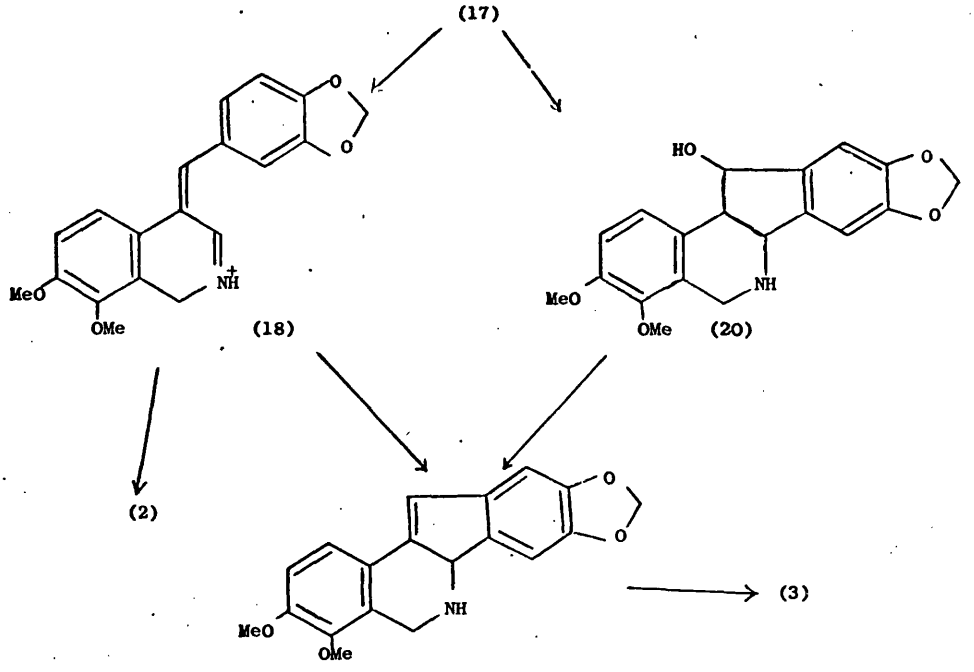


(16) (17) (18) (20)



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2. (a) S.F. Dyke & M. Sainsbury, Tetrahedron, 23, 3161 (1967).
   (b) S.F. Dyke, M. Sainsbury and B.J. Moon, Tetrahedron, 24, 1467 (1968).
   (c) D.W. Brown, S.F. Dyke & M. Sainsbury, Tetrahedron, in the press.

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A NEW BERBINE SYNTHESIS

(Tetrahedron Letters, 1968, 5178)

Tetrahedron Letters No.50, pp. 5177-5178, 1968. Pergamon Press. Printed in Great Britain.

A New Berbine Synthesis

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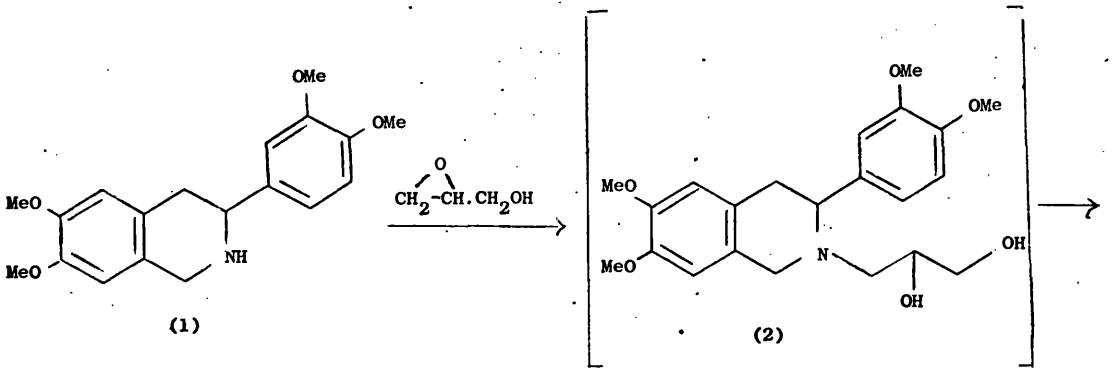
In a continuation of our studies on the synthesis of berbine derivatives[1,2] we now wish to report a new approach which constitutes the first synthesis of 5-hydroxyberbines. The known[3] 3-aryl-1,2,3,4-tetrahydroisoquinoline (1) was reacted with glycidol and the intermediate amino-glycol derivative (2) was, without isolation, oxidised with periodic acid to provide the aldehyde[4] (3). When the latter compound was left in contact with 6N HCl at room temperature for 16 hours, cyclisation occurred and the 5-hydroxyberbine (4) could be isolated in 70% yield as the hydrochloride $C_{21}H_{25}NO_5$.HCl, m.p. 228-229°. The IR spectrum indicated the presence of a hydroxyl group, but was devoid of carbonyl absorption, and the NMR spectrum exhibited resonances attributable to only FOUR aromatic protons. Dehydrogenation of the cyclisation product with iodine gave the quaternary salt (5) and this was easily dehydrated to the known[5] dibenzo[a,g]quinolizium salt (6). Finally, reduction of (6) with sodium borohydride yielded norcoralydine (7), identical with an authentic specimen. The entire sequence of reactions has been repeated with the 3-aryl-1,2,3,4-tetrahydroisoquinoline (8) with similar results.

With this route to 5-hydroxyberbines established, we are currently investigating the synthesis of berberastine (9, R=Me) and thalidastine[7] (9, R=H).



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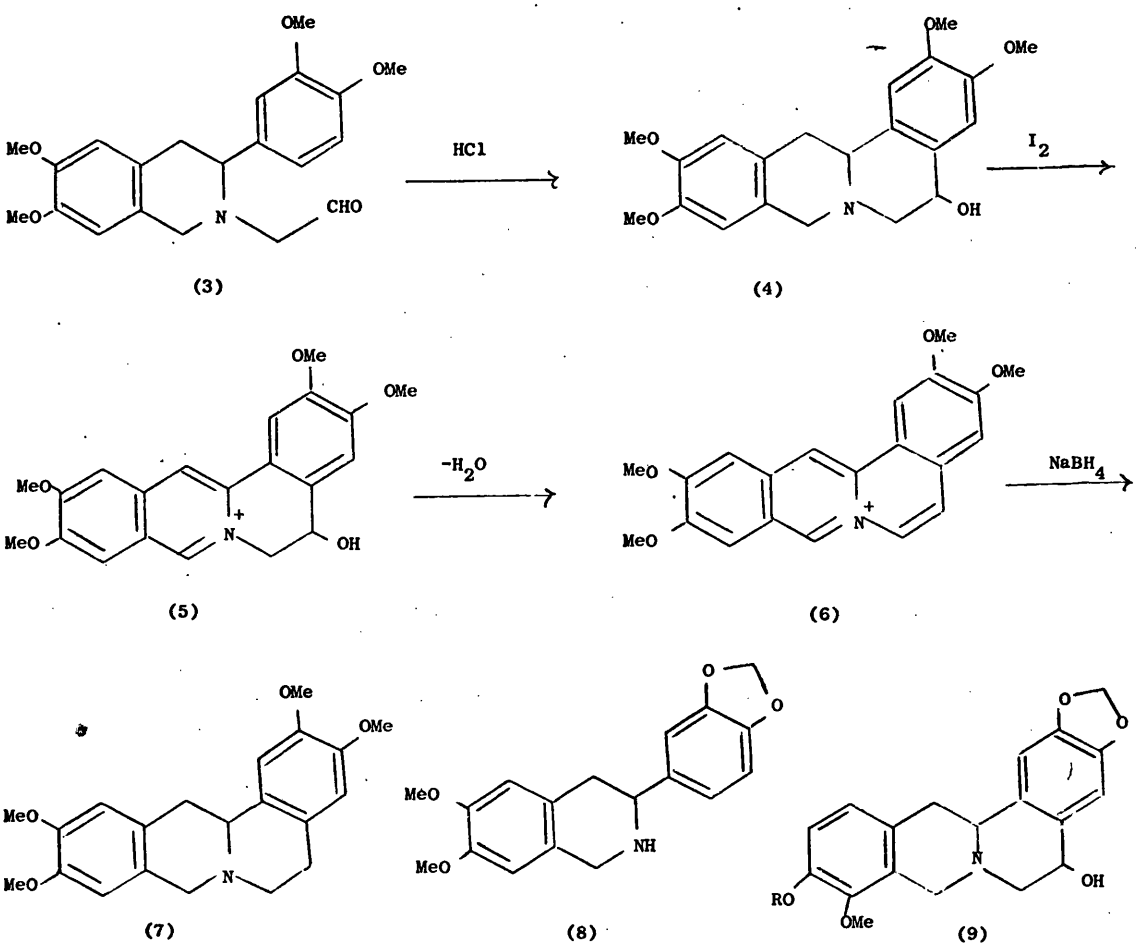

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THE ACTION OF ACIDS ON SOME ACETALDEHYDE DIMETHYLAMINOACETALS

(Tetrahedron Letters, 1968, 2609)

Tetrahedron Letters No.21, pp. 2609-2612, 1968. Pergamon Press. Printed in Great Britain.

THE ACTION OF ACIDS ON SOME SUBSTITUTED ACETALDEHYDE DIMETHYLAMINOACETALS

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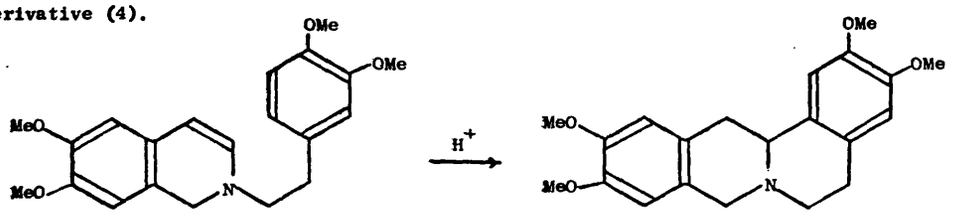
It has been shown[1,2,3] that N-β-arylethyl-1,2-dihydroisoquinolines, such as (1), can be cyclised by acids to berbine derivatives, for example (2), and it is also known[4,5] that the aminoacetaldehyde dialkylacetal (3) can be cyclised by acids to the 1,2-dihydroisoquinoline derivative (4).



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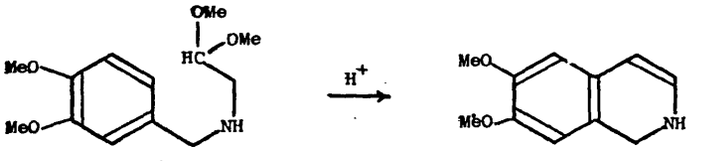
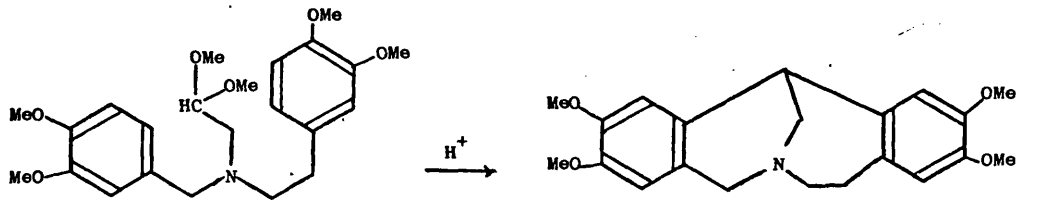


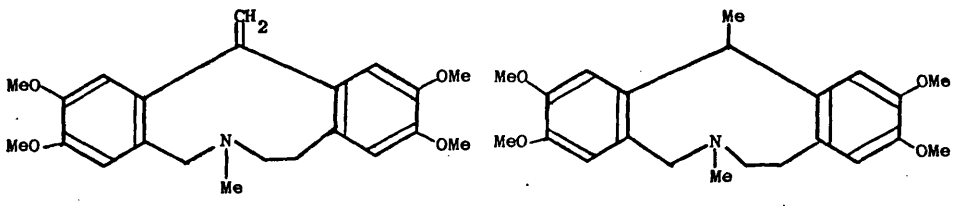
(3) (4)

It occurred to us that a double cyclisation of an appropriately substituted amino-acetaldehyde dimethylacetal such (5) may lead, in a single step, to the berbine skeleton (2). When (5) was treated with conc. HCl for five days at room temperature a base hydrochloride $C_{21}H_{25}NO_4.HCl$ was isolated[6] in 76% yield; its NMR spectrum indicated the presence of only FOUR aromatic protons so that a double cyclisation had indeed occurred. However, it was quickly found that the product differed from a sample of the hydrochloride of (2). The most likely alternative structure (6) is supported by the fact that Hofmann degradation yields a

methine base (7) whose spectral properties indicate the presence of an exocyclic methylene group. Catalytic hydrogenation of (7) proceeded with the uptake of 1 mole gas to give (8)

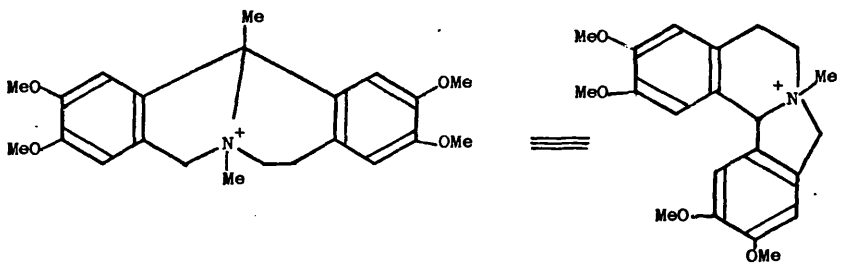


(5) (6)



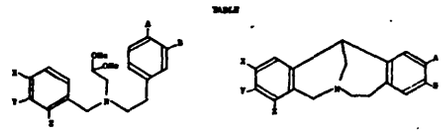
(7) (8)

whose NMR spectrum (taken at 60 Mg/S in $CDCl_3$ solution with internal TMS as reference) contains a three proton doublet centred at 1.7 ppm (J = 6.5 C/S). When the methine (7) was treated with acetic acid, transannular addition to the double bond occurred to yield a quaternary salt (9) whose spectral characteristics are fully consistent with this structure.



(9)

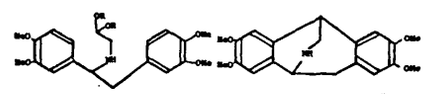
A variety of conditions of acid treatment were studied in an effort to cyclise (5) to the berbine derivative (2), but in each case the product was (6); indeed with phosphoric acid at room temperature for two days, the yield of (6) was raised to 90%. Several differently substituted aminoacetaldehyde dimethylacetals were studied, and in each case structures analogous to (6) were formed. These results are summarised in the TABLE.



TABLE

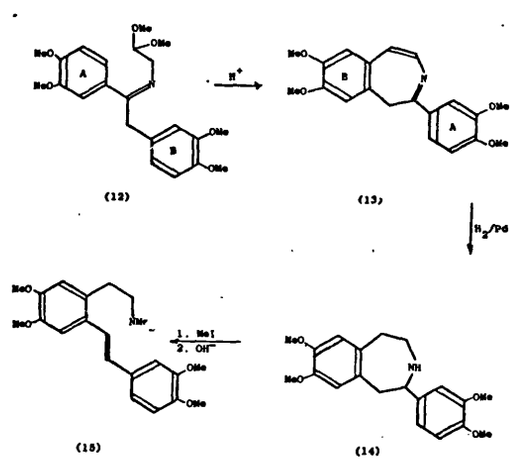
X	Y	Z	A	B	Yield
H	OMe	OMe	OMe	OMe	63
OMe	OMe	H	OMe	OMe	76
H	OMe	OMe	O-CH_2-O		76
OMe	OH	H	OMe	OMe	90
OMe	OMe	H	H	H	0

An analogy for this double cyclisation is provided by the ring-closure of the aminoacetal (10) to the compound (11), termed ISOPAVINE.

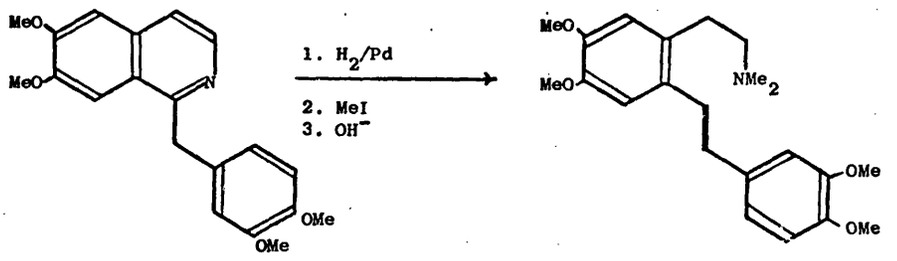


(10) (11)

In 1903 Fritsch[8] reported that when the aminoacetal (12) was treated with conc. H_2SO_4 a base was obtained in 15% yield, and this reaction was re-examined by Guthrie et. al[9] who proposed a structure for this product. However Guthrie's structure was questioned by Battersby and Yoewell[7] who proposed a structure based upon isopavine (11). We have now found that the product described by Fritsch and by Guthrie et. al. can be obtained in 37% yield from (12) by using conc. HCl in place of the conc. H_2SO_4 and that its NMR spectrum can be completely interpreted in terms of structure (13). This deduction was confirmed by the reduction of (13) to a tetrahydro derivative (14) and its degradation to the methine (15), which was shown to be identical with the product obtained from papaverine (16) by reduction and Hofmann degradation.



(12) (13) (15) (14)



(16) (15)

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1,2-DIHYDROISOQUINOLINES - ACYLATION II

(Tetrahedron, 1968, 24, 6703)

Tetrahedron. Vol. 24, pp. 6703 to 6717. Pergamon Press 1968. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—IX[1]

ACYLATION II

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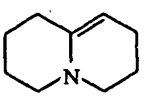
(*Received in the U.K. 4 June* 1968; *accepted for publication* 20 *June* 1968)

Abstract—The reaction between 1,2-dihydroisoquinolines and a variety of acid chlorides is described, and some properties of the resulting 4-acyl-1,2-dihydroisoquinolines are reported.

THE formation of β-diketones by the interaction of an enamine with an acid chloride, in the presence of triethylamine, followed by acid hydrolysis, is now well-known,[2,3] although applications to purely heterocyclic enamines seem to be few. However, the acetylation of **1**[4] and **2**[5] proceed normally to yield the acylated enamines and 5-cyanoindole has[6] been acylated at C_3 by acid chlorides in the presence of stannic chloride. In part IV of this series[7] we described acylation reactions of 2-methyl-1,2-dihydroisoquinoline (**3**) with four acid chlorides, in the presence of triethylamine.



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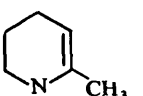
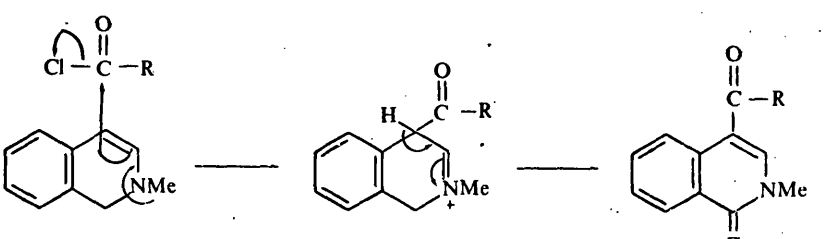


2

The products were the expected acylated enamines, (**4**, Z = H_2) or the related isocarbostyrils (**4**, Z = O) formed from them by aerial oxidation; yields, however, were rather low.



3 **4**

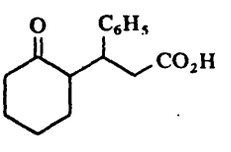
We have now examined the reaction in more detail; we have been able to improve yields considerably, and more closely define the type of acyl compound that can be used. With phenylacetyl chloride in refluxing ether in the presence of one mole of triethylamine we originally[7] obtained **4** (R = $CH_2C_6H_5$, Z = H_2) in only 12% yield, but this is increased to 30% simply by lowering the reaction temperature to 0–5°.

A base other than the enamine itself is necessary to neutralize the HCl formed in the acylation reaction, and we have found that triethylamine functions efficiently in this role. We have not studied the effect of other bases and we have used only ether or benzene as solvents. The interaction of **3** and phenylacetyl perchlorate gave only black tars, whereas no reaction at all was observed when N-benzoylpyridinium chloride was used as the acylating agent. Friedel–Crafts' reactions with $AlCl_3$ or $SnCl_4$ as catalysts also failed. We eventually standardized on the use of an ether solution of **3** and the acid chloride, in the presence of Et_3N, with the temperature held to 0–5° for all of the acid chlorides listed in Table 1. We also examined the use of 2-benzyl-1,2-dihydroisoquinoline as the enamine in some cases, but it offers no real advantage over **3**.

The acylation proceeds most satisfactorily with aromatic acid chlorides, and as may be anticipated, the nitrobenzoyl chlorides gave the highest yields of acylated product, although the reaction failed completely with 6-nitro-3,4-methylenedioxybenzoyl chloride. Unaccountably the reaction failed also with *p*-methoxy, *p*-chloro- and *p*-methylbenzoyl chlorides, whereas acylated enamines were obtained with the 3,4-dimethoxy-, 3,4-dichloro- and 3,4-dimethyl-benzoyl chlorides. The acid chlorides from cinnamic and phenylpropiolic acids also failed to react. It has been reported[8] that cinnamoyl chloride reacts with cyclohexanone enamine in a Michael reaction to yield **5**, but the only acidic compounds isolated with 2-methyl-1,2-dihydroisoquinoline as the enamine were cinnamic and phenylpropiolic acids.

Of the heterocyclic acid chlorides so far examined (indole-3-acetic, thiophene-2-carboxylic and 2-furoic) only 2-furoic acid chloride yielded an acylated enamine.

Acetyl and n-butyryl chlorides failed to yield an acylated enamine with **3**; keten formation is possible as a side reaction with the triethylamine, and presumably **3** is insufficiently reactive to add to these ketens. Pivaloyl chloride, where keten formation is not possible also failed to react with **3**, but chloracetyl chloride worked satisfactorily as did the phenylacetyl chlorides mentioned in Table 1. Acryloyl, crotyl, fumaroyl, methylmalonoyl, methylsuccinoyl chlorides, ethyl chloroformate, pyruvic acid chloride, phenylcarbamoyl, N-methylphenylcarbamoyl chlorides and benzyl-chloroformate all failed to react with 2-methyl-1,2-dihydroisoquinoline. Finally, whereas benzene sulphonyl and *p*-toluenesulphonyl chlorides did not react with **3**, *m*-nitrobenzenesulphonyl chloride gave the vinylogous amide in reasonable yield. β-Ketosulphones have been[9] obtained from cyclohexanone enamines and aromatic



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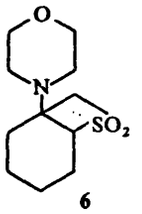


6

sulphonyl chlorides, but with methanesulphonyl chloride aminosulphones of type **6** have been reported.[9–11] Methanesulphonyl chloride did not react with 2-methyl-1,2-dihydroisoquinoline.

Structures for these neutral, acylation products were assigned on the basis of analytical data, spectral properties and chemical reactions. The relevant UV, IR

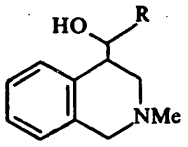
TABLE 1. ACYLATION OF 2-METHYL-1,2-DIHYDROISOQUINOLINE

Acyl Chloride	% Yield*	m.p.°	Molecular formula	Analysis					
				Found			Required		
				C	H	N	C	H	N
C_6H_5COCl	33†	137–138	$C_{17}H_{13}NO_2$	77·8	5·2	5·2	77·55	5·0	5·3
$2\text{-}NO_2C_6H_4COCl$	65	219–222	$C_{17}H_{14}N_2O_3$	68·8	4·8	9·7	69·4	4·8	9·5
$3\text{-}NO_2C_6H_4COCl$	85	168–170	$C_{17}H_{14}N_2O_3$	68·7	4·7	9·8	69·4	4·8	9·5
$4\text{-}NO_2C_6H_4COCl$	73	193–196	$C_{17}H_{14}N_2O_3$	68·7	4·7	9·8	69·4	4·8	9·5
$2\text{-}NO_2\text{-}3\text{-}OMeC_6H_3COCl$	5	186–187	$C_{18}H_{16}N_2O_4$	66·7	4·8	8·8	66·6	4·9	8·6
$3,4\text{-}(MeO)_2C_6H_3COCl$	33	148–150	$C_{19}H_{19}NO_3$	73·7	6·1	4·35	73·8	6·2	4·5
$3,4\text{-}Cl_2C_6H_3COCl$	11	170–171	$C_{17}H_{13}NOCl_2$	64·1	4·0	3·8	64·2	4·1	4·4
$3,4\text{-}Me_2C_6H_3COCl$	14	143–144	$C_{19}H_{19}NO$	81·6	6·9	4·5	82·3	6·9	5·1
$C_6H_5CH_2COCl$	30	112–113	$C_{18}H_{17}NO$	82·1	6·5	5·2	82·1	6·5	5·3
$2\text{-}NO_2C_6H_4CH_2COCl$	20	217–219	$C_{18}H_{16}N_2O_3$	70·1	5·2	9·1	70·2	5·3	9·2
$3,4\text{-}(MeO)_2C_6H_3CH_2COCl$	14	112–114	$C_{20}H_{21}NO_3$	73·9	6·6	4·5	74·3	6·55	4·3
2-Furoyl chloride	33	71–72	$C_{15}H_{13}NO_2$	74·0	5·2	5·9	73·3	5·5	5·9
$ClCH_2COCl$	20	94–95	$C_{12}H_{12}NOCl$	64·8	5·4	5·7	65·0	5·4	6·3
$EtO_2C\cdot COCl$	21	131–132	$C_{14}H_{15}NO_3$	68·5	6·0	5·5	68·6	6·2	5·7
$3\text{-}NO_2C_6H_4SO_2Cl$	28	117–119	$C_{16}H_{14}N_2O_4S$	59·1	4·5	9·1	58·2	4·2	8·5

* From isoquinoline methiodide. † The isocarbostyril.

and NMR spectral data are summarized in Table 2, and Fig. 1 illustrates a typical NMR spectrum in this series.

7



8

All the IR carbonyl frequencies are low, in agreement with other experience[13,14] with vinylogous amides. Some of the 4-acyl-1,2-dihydroisoquinolines (4, Z = H_2) reacted with perchloric acid to give the O-perchlorate, in agreement with previous work,[7,15] and in several cases the acylated enamines were oxidized with perchloric acid, or better with iodine, to the fully aromatic isoquinolinium salts (7). UV spectra for these quaternary salts were characteristic of the isoquinolinium cation, and the NMR spectra were found to be diagnostic for 4-substituted-2-methylisoquinolinium salts[12] (see Table 3 and Fig. 2). The reduction of some of the acylated enamines mentioned in Table 1 was examined, using both LAH and $NaBH_4$. For those compounds containing a nitro group the reduction reaction was a complicated one and will be described in a later paper, but in the other cases examined reduction of the carbonyl group and the Δ^3 double bond occurred with both reagents to yield the 1,2,3,4-tetrahydroisoquinoline alcohols (8). This is contrary to other experience[16,17] on the reduction of enamino ketones with LAH.

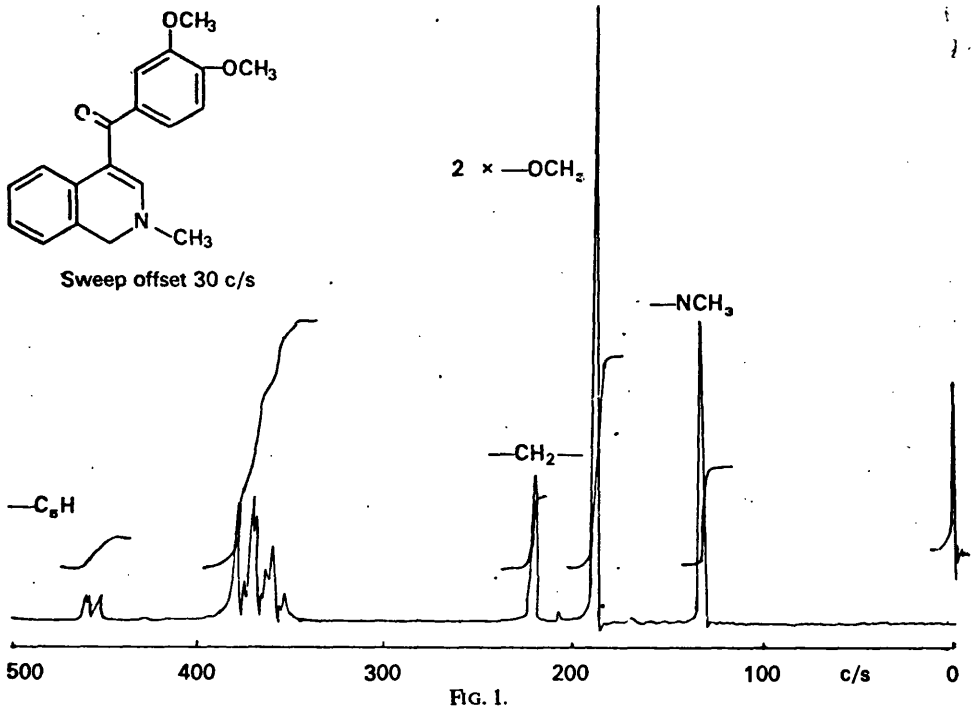


FIG. 1.

TABLE 2. SPECTRA DATA FOR THE ACYLATED ENAMINES (4, Z = H_2)

Acyl group	UV		IR	NMR				
	λ_{max} mμ	ε_{max}	ν cm^{-1}	Solvent	Ar—$C\underline{H}_2$—N	NMe	C_5H (multiplet)	Others
2-$NO_2C_6H_4CO$	208 284 343	15,350 4305 4500	1630 1600	CD_3SOCD_3	4·65	3·00		
3-$NO_2C_6H_4CO$	220 345	10,880 1090	1630 1570	$CDCl_3$	4·55	3·00		
4-$NO_2C_6H_4CO$	205 283 340	16,070 9330 4670	1620 1590	CF_3CO_2H	5·1	3·7		
2-NO_2-3-OMe-C_6H_3CO	208	32,400	1620 1600 1580	CD_3SOCD_3	4·64	3·06		3·95 OMe
3,4-$(OMe)_2C_6H_3CO$	208 225 305 340	19,340 13,880 10,180 8120	1620 1600 1560	$CDCl_3$	4·20	2·7	8·1	3·65 2 × OMe
3,4-$Cl_2C_6H_3CO$	206 340	21,130 8450	1620 1580	$CDCl_3$	4·50	2·92	8·5	
3,4-$Me_2C_6H_3CO$	204 320	13,380 6150	1620 1600 1580	$CDCl_3$	4·40	2·80	8·5	2·25 2 × Ar—CH_3

Table 2—continued

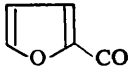
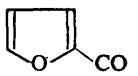
$C_6H_5CH_2CO$	208 225 290 340	21,400 14,500 14,640 12,390	1630 1600 1570	$CDCl_3$	4·00	2·50	8·33	3·75—CH_2CO
2-NO_2 $C_6H_4CH_2CO$	212 285 345	5900 2900 2000	1640 1590	CF_3CO_2H	4·84	3·67		4·5 CH_2 COAr
3,4-$(OMe)_2$ $C_6H_3CH_2CO$	230 287 345	25,120 23,990 18,200	1625 1605 1580	$CDCl_3$	4·40	3·00	7·5	3·95 CH_2CO + 2 × OCH_3
	230 275 315 365	25,190 17,855 24,495 24,495	1620 1595	$CDCl_3$	4·10	2·80	8·1	
$ClCH_2CO$	215 230 300 352	5475 5900 6120 6350	1640 1600 1580	$CDCl_3$	4·20	3·00	8·7	4·43 $COCH_2Cl$
EtO_2C CO	210 228 300 350	7915 8130 6478 7205	1715 1630 1570	$CDCl_3$	5·30	3·00	8·6	5·2q $\underline{CH_2}CH_3$ 1·5t CH_2—$\underline{CH_3}$
3-NO_2—$C_6H_4SO_2$	207 240 255 327	20,840 17,440 14,880 7030	1610 1600 1560	CD_3SOCD_3	4·55	2·94		

TABLE 3. UV AND NMR SPECTRA DATA FOR THE ISOQUINOLINIUM SALTS

C_4-Acyl group	UV		NMR				
	λ_{max} mμ	ε_{max}	Solvent	C_1H	C_3H	NMe	Others
2-$NO_2C_6H_4CO$	216	30,800	CD_3SOCD_3	10·22	8·90	4·55	
3-$NO_2C_6H_4CO$	219 340	40,000 6200	CD_3SOCD_3	10·30	9·00	4·33	
4-$NO_2C_6H_4CO$	205 279	25,000 1300	CD_3SOCD_3	10·20	9·00	4·55	
3,4-$(OMe)_2C_6H_3CO$	205 235 290 335	29,300 43,750 12,250 13,130	CF_3CO_2H	9·25	8·10	4·50	4·05 2 × OCH_3
$C_6H_5CH_2CO$	220 265 335	37,200 4180 7500	CF_3CO_2H	9·67	9·00	4·60	4·65 —CH_2CO—
	235 295 340	39,700 18,240 16,000	CF_3CO_2H	9·50	8·40	4·50	

A chemical proof of structure of these 4-acyl-1,2-dihydroisoquinolines was forthcoming by utilising the observation of Gilman and Soddy[18] that 4-bromoisoquinoline reacts with n-butyllithium at low temperatures to form 4-lithioisoquinoline. Thus, reaction of this organometallic compound with 3,4-dimethoxybenzaldehyde yielded the alcohol **9**, isolated as its O-acetylmethiodide. Reduction of this derivative with LAH gave **8** (R = 3,4-dimethoxyphenyl), identical with the product formed by the reduction of **4** (R = 3,4-dimethoxyphenyl, Z = H_2) with the same reagent.

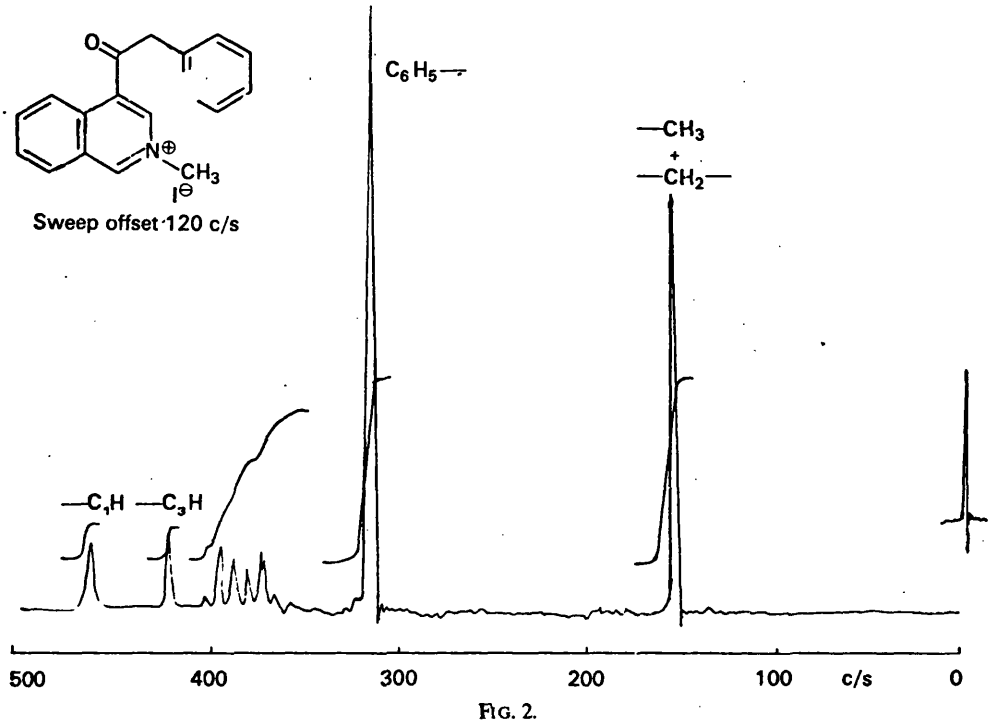
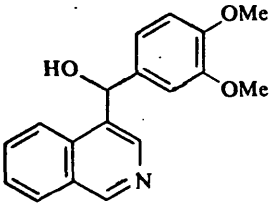
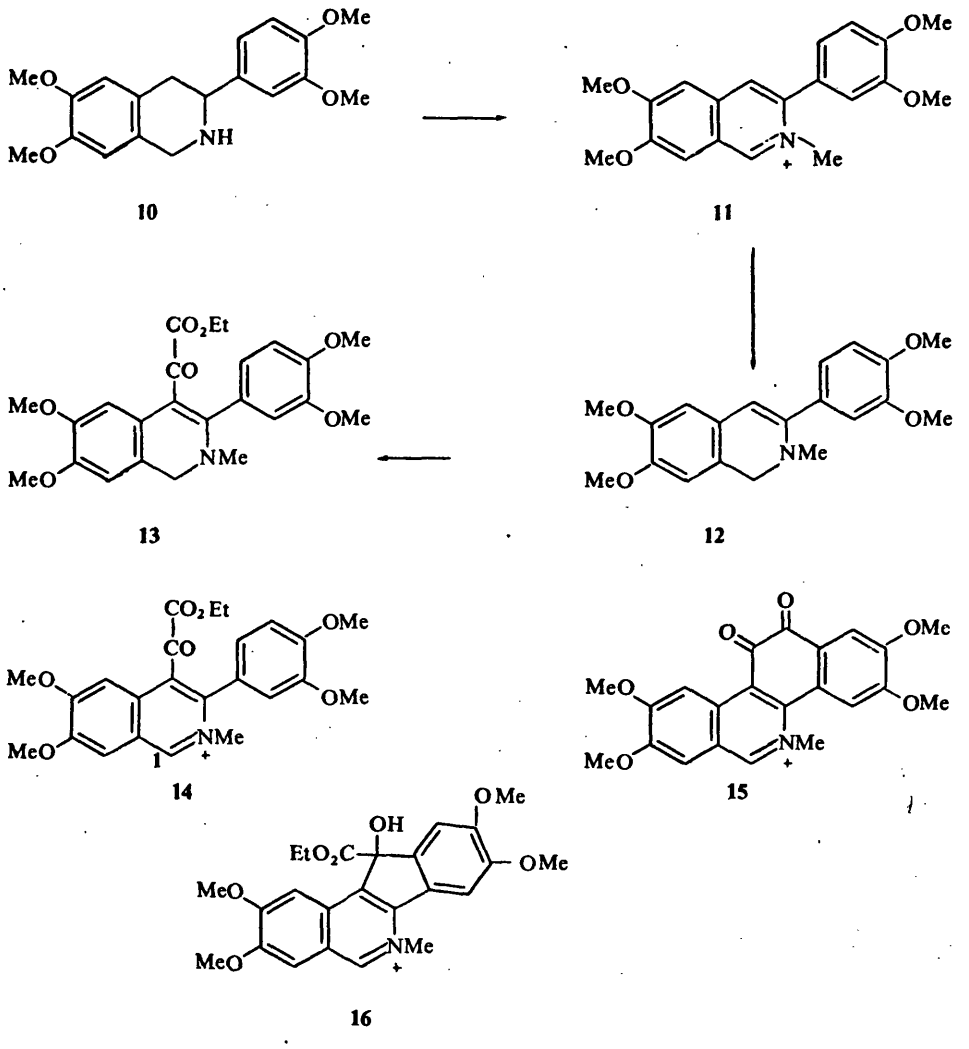


FIG. 2.

Our interest in benzo[c]phenanthridine chemistry[19,20] stimulated a study of some acylation reactions of the 2-methyl-3-aryl-1,2-dihydroisoquinoline (**12**), which was prepared as indicated from the known[21] 1,2,3,4-tetrahydroisoquinoline (**10**). The interaction of **12** with ethoxalyl chloride gave a low yield of the acylated enamine **13**, which was easily oxidized to, and further characterized as, the isoquinolinium salt **14**. Various attempts were made to cyclize **14** to **15**, but the only product isolated was assigned structure **16** on the basis of its analysis and spectral characteristics.

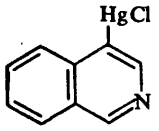


9

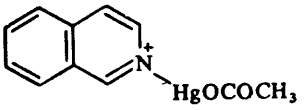


Other methods of acylation of 2-methyl-1,2-dihydroisoquinoline have been briefly examined. When isoquinoline is treated with mercuric acetate, then with sodium chloride, the product is reported[22] to be **17**, on the grounds that bromination yields 4-bromo-isoquinoline, and we hoped to be able to acylate this compound. However, we found that the NMR spectrum of the intermediate mercuriacetate derivative is completely consistent with its formulation as **18** and not as a 4-substituted isoquinoline. Thus, the spectrum (in $CDCl_3$ soln) exhibited a one proton singlet at 9·4 ppm (C_1—H), a one proton *doublet* at 8·7 ppm (J = 6·5 c/s) (C_3—H) and a three proton singlet at 2·1 ppm (CH_3CO—). Since the C_3—H absorption appears as a doublet, there must be a hydrogen atom at C_4 of the isoquinoline ring. A molecular weight determination in cyclohexanol is also consistent with structure **18**.

The Vilsmeier formylation reaction is well known,[23,24] and our application of it to 1,2-dihydroisoquinolines will be described in detail in a later paper. The acylation



17



18

reaction using a tertiary acid amide in place of dimethylformamide is not so common, although some 3-acylindoles have been prepared by this method.[25] We have now found that 2-methyl-1,2-dihydroisoquinoline (3) reacts with N,N-dimethylacetamide, in the presence of $POCl_3$, to form the corresponding acylated enamine (4, R = CH_3, Z = H_2) in 36% yield.

EXPERIMENTAL

UV spectra were measured on a Perkin–Elmer Model 137UV spectrophotometer and refer to EtOH solns unless otherwise stated. IR spectra were measured, in Nujol, on a Perkin–Elmer Model 237 spectrophotometer. NMR spectra were recorded with a Varian A-60 spectrometer and chemical shifts are measured in ppm downfield from internal TMS as standard. M.ps are uncorrected.

2-Methyl-1,2-dihydroisoquinoline (3) was prepared as previously described[7] and *2-benzyl-1,2-dihydroisoquinoline* was prepared similarly.

Acylations

General procedure. The acid chloride (0·04 mole), in ether or benzene soln, was added dropwise to a stirred soln of 2-methyl-1,2-dihydroisoquinoline (0·04 moles) in ether containing Et_3N (4·0 g). An atmosphere of N_2 was maintained in the reaction flask throughout. After 3 more hr of stirring, during which time a considerable amount of ether evaporated, thus keeping the temp to 0–5°, the reaction mixture was left overnight, then filtered. The solid was stirred well with water (75 ml) and the undissolved residue of 4-acyl-1,2-dihydroisoquinoline was crystallized, usually from EtOH. The relevant data are collected into Table 1.

The O-perchlorates were prepared simply by adding 60% aqueous perchloric acid soln to a soln of the acylated enamine (4, Z = H_2) in EtOH soln. The precipitated perchlorate was collected and crystallized.

(a) From 2-methyl-4-(2-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 131–132°; λ_{max} (ε) mμ, 208 (12,350), 283 (3642), 345 (4265). ν_{max} cm^{-1}, 3500, 1660, 1590. NMR (CD_3SOCD_3) 3H singlet 3·0 (=$NC\underline{H}_3$); 2H singlet 4·6 (Ar—$C\underline{H}_2$—N=). (Found: C, 51·1; H, 3·7; N, 7·1. $C_{17}H_{15}N_2ClO_7$ requires: C, 51·7; H, 3·8; N, 7·1%).

(b) From 2-methyl-4-(3-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 170–171°; λ_{max} mμ (ε_{max}) 222 (12,160), 345 (3200); ν_{max} cm^{-1} 3220, 1662, 1595. NMR (CD_3SOCD_3); 3H singlet 3·0 (=$NC\underline{H}_3$); 2H singlet 4·65 (Ar—$C\underline{H}_2$—N<); 1H singlet 5·9 removed by D_2O (—O<u>H</u>); 9H multiplet ca. 8·0 (aromatic hydrogens). (Found: C, 51·9; H, 3·7; N, 8·1%).

(c) From 2-methyl-4-(4-nitrobenzoyl)-1,2-dihydroisoquinoline m.p. 151–152°; λ_{max} mμ (ε_{max}): 205 (8217); 285 (6575); 340 (2300); ν_{max} cm^{-1}: 3430, 1670, 1590; NMR (CD_3SOCD_3), 3H singlet 3·0 (=$NC\underline{H}_3$); 2H singlet 4·6 (Ar—$C\underline{H}_2$N=). (Found: C, 49·9; H, 4·0; N, 6·8%).

The isoquinolinium salts

(a) In some cases, treatment of the acylated enamine with perchloric acid yielded, not the O-perchlorate, but the fully aromatic isoquinolinium perchlorate.

(a)′ 2-methyl-4-(3,4-dimethoxybenzoyl) isoquinolinium perchlorate m.p. 236–238° λ_{max} (ε) mμ, 205 (29,300); 235 (43,750); 290 (12,250); 335 (13,130); ν_{max} cm^{-1}, 1655, 1595, 1580, 1510, 1100; NMR (CF_3CO_2H) 1H singlet 9·25 (C_1—H); 1H singlet 8·1 (C_3—H) 3H singlet 4·5 (=$NC\underline{H}_3$); 6H singlet 4·05 (2 × —$OC\underline{H}_3$). (Found: C, 51·4; H, 4·3; N, 3·5; Cl, 8·7. $C_{19}H_{18}NO_7Cl$ requires: C, 51·0; H, 4·3; N, 3·4; Cl, 8·7%).

(b)′ 2-Methyl-4-(α-furoyl)isoquinolinium perchlorate m.p. 162–163°; λ_{max} (ε) mμ, 235 (21,000); 290 (4080); 340 (3460); ν_{max} cm^{-1}, 1650, 1610, 1100; NMR (in CF_3CO_2H) 1H singlet 9·7 (C_1—<u>H</u>); 1H singlet 8·78

($C_3\underline{H}$); 3H singlet 4·8 (=N—$C\underline{H}_3$). (Found: C, 53·6; H, 3·5; N, 4·1; Cl, 11·0. $C_{15}H_{12}NO_6Cl$ requires: C, 53·35; H, 3·55; N, 4·15; Cl, 10·5%).

(b) A more satisfactory method of oxidation of the acylated enamine to the isoquinolinium salt involved heating under reflux a mixture of the acylated enamine (1·0 g), EtOH (50 ml), and I_2 (1·0 g) for 3 hr. Water (20 ml) was then added and SO_2 passed through the mixture until only a straw colour remained. Concentration of the soln caused crystallization of the isoquinolinium iodide, which was then recrystallized from EtOH. The data are summarized in Table 4.

2-Methyl-4-[1-hydroxy-2-(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline

Compound **4** (Z = H_2, R = 3,4-dimethoxyphenyl) in EtOH (25 ml) was treated with $NaBH_4$ (1·0 g) in small portions. The mixture was heated under reflux for 2 hr, cooled and water (50 ml) was added. The soln was extracted with $CHCl_3$ (3 × 25 ml) and the combined extracts were evaporated to leave a yellow gum which crystallized from EtOH to give 2-methyl-4-[1-hydroxy-2-(3,4-dimethoxy)phenylethyl]-1,2,3,4-tetrahydroisoquinoline (0·81 g) m.p. 158–160°; λ_{max} (ε) mμ, 206 (35,100); ν_{max} cm^{-1}, 1610; 1590. (Found: C, 72·6; H, 7·4; N, 4·4. $C_{19}H_{23}NO_3$ requires: C, 72·8; H, 7·35; N, 4·5%).

4-[-1-Hydroxy-1-(α-furyl)]methyl-2-methyl-1,2,3,4-tetrahydroisoquinoline

This was prepared by reduction of **4** (R = 2-furyl, Z = H_2) with $NaBH_4$ at room temp during 18 hr and was obtained crystalline from MeOH m.p. 103–104°; λ_{max} (ε) mμ, 217 (14,850). (Found: C, 73·9; H, 7·1; N, 5·9. $C_{15}H_{17}NO_2$ requires: C, 74·05; H, 7·0; N, 5·8%). The O-acetate was obtained from EtOH, m.p. 60–61° and this was analysed as the methoperchlorate m.p. 180–181°. (Found: C, 53·5; H, 5·4; N, N, 3·4; Cl, 8·4. $C_{18}H_{24}NO_7Cl$ requires: C, 54·1; H, 5·5; N, 3·5; Cl, 8·9%).

Acylation of 2-benzyl-1,2-dihydroisoquinoline

This was carried out essentially as described for 2-methyl-1,2-dihydroisoquinoline, and the relevant data are collected into Table 5. In *all* cases studied, the product was the acylated enamine.

The product with furoyl chloride was further characterized by oxidation with I_2 in the usual way to yield 2-benzyl-4-furoylisoquinolinium iodide m.p. 122–124°; λ_{max} (ε) mμ, 240 (44,330); 293 (31,680); 350 (15,200). ν_{max} cm^{-1}, 1640; NMR in CD_3SOCD_3, 1H singlet 10·03 (C_1—$\underline{H}$); 1H singlet 8·9 (C_3—$\underline{H}$); 1H multiplet 8·22 (C_5—$\underline{H}$); 2H singlet 5·9 (Ar—$C\underline{H}_2$—$\overset{+}{N}$≡). (Found: C, 57·35; H, 3·6; N, 3·0; I, 28·9. $C_{21}H_{16}NO_2I$ requires: C, 57·2; H, 3·6; N, 3·2; I, 28·8%).

The 1,2,3,4-tetrahydroisoquinoline was prepared by reducing the vinylogous amide with $NaBH_4$ and was obtained as white crystals from EtOH m.p. 111–113°. (Found: C, 78·8; H, 6·9; N, 4·6. $C_{21}H_{21}NO_2$ requires: C, 79·0; H, 6·6; N, 3·4%). This compound was further characterized as the O-acetate, m.p. 123–124°. (Found: C, 75·8; H, 6·4; N, 4·1. $C_{23}H_{23}NO_3$ requires: C, 76·4; H, 6·4; N, 3·9%).

4-[1-Hydroxy-1-(3,4-dimethoxyphenyl)methyl]isoquinoline (**9**, R = *3,4-dimethoxyphenyl*)

A soln of veratraldehyde (4·1 g) in dry ether (100 ml) was added dropwise with stirring during 20 min to a soln of 4-isoquinolyllithium (prepared[18] from 5·2 g 4-bromoisoquinoline) in dry ether (50 ml) maintained at −50°. After 2 hr stirring the mixture was treated with NH_4Cl aq, the ether layer was separated, washed and dried ($MgSO_4$). Evaporation left a red oil which could not be crystallized. Ac_2O (15 ml) was added and the mixture was warmed on the water-bath for 20 min. After working up in the usual way, the red, oily product was heated under reflux with an excess of MeI for 15 min. After evaporation of the soln and crystallization of the residue from EtOH, 2-methyl-4-[1-acetoxy-1-(3,4-dimethoxyphenyl)methyl]-isoquinolinium iodide was obtained (7 g; 45%) as yellow needles m.p. 220–221°; λ_{max} (ε) mμ, 204 (41,870); 232 (36,630) ν_{max} cm^{-1}, 1750, 1650, 1600, 1025; NMR (CD_3SOCD_3), 1H singlet 10·25 ppm (C_1—$\underline{H}$), 1H singlet 9·0 ppm (C_3—$\underline{H}$); 3H singlet 4·66 ppm ($\overset{+}{N}$≡—$C\underline{H}_3$); 3H singlets at 3·83 and 3·76 ppm (2 × $OC\underline{H}_3$); 3H singlet 2·3 ppm ($C\underline{H}_3$ CO—). (Found: C, 52·3; H, 4·8; N, 3·5. $C_{23}H_{25}NO_6I$ requires: C, 52·6; H, 4·6; N, 2·9%).

2-Methyl-4-[1-hydroxy-1-(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline (**8**, R = *3,4-dimethoxyphenyl*

The above methiodide (1·0 g) was dissolved in boiling dry benzene (150 ml) and LAH (1 g) was added portionwise. The mixture was heated under reflux for 2 hr, and then worked up in the usual way to yield **8**, (R = 3, 4-dimethoxyphenyl) as white needles from EtOH. (0·65 g) m.p. 159–160°; mixed m.p. with material obtained by reducing **4** (R = 3,4-dimethoxyphenyl) with LAH = 159°.

TABLE 4. THE ISOQUINOLINIUM IODIDES

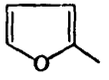
4-Acyl Group	m.p.°	Molecular Formula	Analysis							
			Found				Required			
			C	H	N	I	C	H	N	I
$C_6H_5CH_2$—	191–193	$C_{18}H_{16}NOI$	53·6	3·8	3·5	32·1	53·3	3·95	3·5	31·4
2-$NO_2C_6H_4$—	167–168	$C_{17}H_{13}N_2O_3I$	48·15	3·4	6·8	—	48·7	3·1	6·65	—
3-$NO_2C_6H_4$—	233–234	$C_{17}H_{13}N_2O_3I$	48·5	3·35	6·65	—	48·7	3·1	6·65	
4-$NO_2C_6H_4$—	207–208	$C_{17}H_{13}N_2O_3I$	48·2	3·0	6·8		48·7	3·1	6·65	
	215–216	$C_{15}H_{12}NO_2I$	49·5	3·2	3·8	34·9	49·3	3·3	3·8	34·8

TABLE 5. ACYLATION OF 2-BENZYL-1,2-DIHYDROISOQUINOLINE

Acyl Chloride	Yield %	m.p.°	λ_{max} mμ	ε_{max}	ν_{max} cm^{-1}	Molecular formula	Found			Required		
							C	H	N	C	H	N
C_6H_5COCl	36	128–129	207 227 307 350	25,400 18,700 11,900 13,050	1625 1600 1585	$C_{23}H_{19}NO$	85·7	6·1	4·5	84·9	5·9	4·3
$3\text{-}NO_2—C_6H_4COCl$	69	136–138	207 222 350	19,260 17,000 8610	1610 1580 1530	$C_{23}H_{18}N_2O_3$	74·8	4·7	7·7	74·6	4·9	7·6
$4\text{-}NO_2—C_6H_4COCl$	75	163–164	207 274 340	31,500 20,000 12,900	1610 1575	$C_{23}H_{18}N_2O_3$	75·1	4·8	8·1	74·6	4·9	7·6
2-Furoyl	34		237 280 316 370	14,400 10,860 14,400 15,470	1620 1570 1540	$C_{21}H_{17}NO_2$	79·6	5·0	4·6	80·0	5·4	4·4

3-(3,4-Dimethoxyphenyl)6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline (**12**)

The methiodide **11**, yellow needles m.p. 248–250 (from EtOH), was reduced with LAH in the normal way to give the corresponding **12** in 80% yield. Recrystallization of this material from THF afforded colourless prisms, m.p. 118–120°; λ_{max} (ε) mμ, 254 (10, 720), 342 (17,580); ν_{max} cm^{-1}, 1645; NMR, ($CDCl_3$) 2H singlet 7·1 (C_5—H, C_8—H); 3H complex ~6·6 (three protons of 3-aryl group); 1H singlet 5·9 (C_4—H); 2H singlet 4·2 (—CH_2—N=) 12H three singlets ~3·9. (4 × —OCH_3); 3H singlet 2·5 (=N—CH_3). (Found: C, 70·1; H, 6·8; N, 4·4. $C_{20}H_{23}NO_4$ requires: C, 70·4; H, 6·8; N, 4·1%).

3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-4-ethoxalyl-2-methyl-1,2-dihydroisoquinoline (**13**)

The foregoing 1,2-dihydroisoquinoline (1·87 g) in benzene, containing Et_3N (0·55 g), was treated with ethoxalylchloride (0·75 g) during 1 hr. the reaction mixture being protected by an atmosphere of N_2. After heating at reflux for 2 hr, the contents of the flask were cooled and EtOAc (100 ml) added. The solvent layer was washed with water, dried and the solvent removed to yield a gum, which crystallized on trituration with 1:1 benzene, light petrol and recrystallized from EtOH as colourless prisms, m.p. 146–148° (29%); λ_{max} (ε) mμ, 232 (10,470), 301 (8510); ν_{max} cm^{-1}, 1700, 1640, NMR ($CDCl_3$), 1H singlet 8·3 (C_5—H); 3H singlet 6·9 (three protons on 3-aryl group); 1H singlet 6·5 (C_8—H); 2H singlet 4·5 (CH_2—N=), 12H singlet 3·9 (4 × —OCH_3); 2H quartet 3·4 J = 8 c/s (—CH_2—CH_3); 3H singlet 2·9 (=N—CH_3); 3H triplet 1·1 J = 8 c/s (—CH_2—CH_3). (Found: C, 64·9; H, 6·0; N, 3·4. $C_{24}H_{27}NO_7$ requires: C, 65·3; H, 6·2; N, 3·2%).

Oxidation of this compound with I_2 in EtOH soln gave **14** in almost quantitative yield, as yellow needles m.p. 199·5–201·5° (EtOH); λ_{max} (ε) mμ, 221 (10,900); 257 (57,540); ν_{max} cm^{-1}, 1745, 1720, 1620, 1610. (Found: C, 50·0; H, 4·8; N, 2·6; I, 22·3. $C_{24}H_{26}NO_7I$ requires: C, 50·8; H, 4·6; N, 2·5; I, 22·4%).

The corresponding isocarbostyril was also isolated as an almost colourless solid m.p. 199–200° (from EtOH) when solns of **13** were allowed to stand in contact with the air. (Found: C, 63·1; H, 5·8; N, 3·0. $C_{24}H_{25}NO_8$ requires: C, 63·3; H, 5·5; N, 3·1%).

Catalytic hydrogenation of **14** in EtOH soln using Adams' catalyst at atm press gave the corresponding 1,2,3,4-tetrahydroisoquinoline, colourless solid m.p. 146–148° (EtOH); λ_{max} (ε) mμ, 232 (10,960), 301 (850); ν_{max} cm^{-1}, 1700. (Found: C, 64·9; H, 6·2; N, 3·35. $C_{24}H_{29}NO_{07}$ requires: C, 65·0; H, 6·6; N, 3·2%).

Reaction of (**14**) *with polyphosphoric acid*

Compound **14** was heated with five times its weight of polyphosphoric acid at 60° for 20 min, after cooling for 20 min, the reaction mixture was poured onto ice and the solid product collected. After crystallization from MeOH this material m.p. 250–251° was dissolved in MeOH and perchloric acid added. 2 Hr later, the yellow crystals which had deposited, were collected and recrystallized from water to give 11-carboethoxy-11-hydroxy-6-methyl-2,3,8,9-tetramethoxy-11-H indeno [1,2—C]isoquinolinium iodide. m.p. 299–299·5° (20%); λ_{max} (ε) mμ, 261 (14,790), 308 (1690); ν_{max} cm^{-1} 3400, 1740, 1625, 1620, 1100; NMR (CF_3CO_2H), 1H singlet 9·0 (C_5—H); 2H singlet 7·7 (C_1—H, C_4—H); 2H singlet 7·5 (C_{10}—H, C_7—H); 3H singlet 4·8 (=N—CH_3); 14H complex 4·2–3·8 (—CH_2—CH_3. 4 × OCH_3); 3H triplet 1·0, J = 7 c/s (CH_3CH_2—). (Found: C, 52·9; H, 4·6; N, 2·9; Cl, 6·8. $C_{24}H_{26}NO_{11}Cl$ requires: C, 53·4, H, 4·9; N, 2·6; Cl, 6·6%).

Reaction of isoquinoline with mercuric acetate

A mixture of isoquinoline (13 g) in MeOH (100 ml) and mercuric acetate (32 g) was heated under reflux for 4 hr as previously described.[19] On concentration and cooling of the soln, the mercuric acetate complex **18** crystallized (38 g), m.p. 131–133° (Lit.[22] m.p. 131–133); λ_{max} mμ (ε_{max}): 217 (62,100) ν_{max} cm^{-1}: 1630, 1580; NMR (in $CDCl_3$): 1H singlet 9·4 (C_1—H); 1H *doublet* 8·7 (J = 6·5 c/s) (C_3—H); 5H multiplet 7·2–8·0 (C_5H, C_6H, C_7H, C_8H, C_4H); 3H singlet 2·1 ($COCH_3$). [Found: C, 35·0; H, 3·6; N, 3·6. $C_{11}H_{10}NO_2$ Hg requires: C, 34·4; H, 2·6; N, 3·0%; Mol. wt. (in cyclohexanol). Found: 397. Calc. 389].

2-Methyl-4-acetyl-1,2-dihydroisoquinoline (**4**, R = Me, Z = 2H)

$POCl_3$ (5 ml) and N,N-dimethylacetamide (28 ml) were mixed together so that the temp did not rise above 20°. To this mixture was added a soln of 2-methyl-1,2-dihydroisoquinoline (5·5 g) in ether (50 ml) under a protective atmosphere of N_2. After heating for 2 hr at the reflux, the reaction mixture was cooled, added to water (50 ml) and made alkaline with NaOH (40·0 g) in water (150 ml). The following morning the two phase system was treated with $CHCl_3$ and the solvent layer removed and evaporated to give a red gum (2·7 g) which did not crystallize; λ_{max} (ε) mμ, 225 (8150), 285 (6440), 345 (6440); ν_{max} cm^{-1}, 1630 (>C=O), 1600 (>C=C<), 1350 (CH_3CO); NMR (in $CDCl_3$) 1H multiplet 8·6 (C_5—H); 4H multiplet,

6·9—7·3 (C_3—H, C_6—H, C_7—H, C_8—H); 2H singlet, 4·4 (>N—$\underline{CH}_2$—Ar); 3H singlet, 3·0 (>N—$\underline{CH}_3$); 3H singlet, 2·3 ($\underline{CH}_3$—CO—). The perchlorate was prepared as colourless prisms, m.p. 166–168° (from EtOH); ν_{max} cm^{-1}, 3500 (OH), 1660 (>C=C<), 1350, 1100. (Found: C, 50·5; H, 4·9; N, 4·9. $C_{12}H_{14}NO_5Cl$ requires: C, 50·1; H, 4·9; N, 4·9%).

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THE CYCLISATION OF

BENZYLAMINOACETALDEHYDE DIALKYLACETALS

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1,2-DIHYDROISOQUINOLINES X[1]

THE CYCLIZATION OF BENZYLAMINOACETALDEHYDE DIALKYLACETALS

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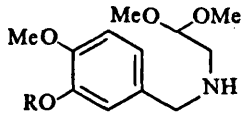
Abstract—The cyclization of some benzylaminoacetaldehyde dialkyl acetals has been examined and their utilization for the preparation of various isoquinoline derivatives studied. Some observations on the mechanism of cyclization of these acetals have also been made.

THE Pomeranz–Fritsch synthesis of isoquinolines involves[2] the cyclization of N-benzylaminoacetaldehyde dialkyl acetals with sulphuric acid, and the method has the great attractions that the fully aromatic isoquinoline is formed directly, and that the orientation of substituents in the product can differ from that obtained by the more common Bischler–Napieralski[3] reaction. There are serious disadvantages, however, and the method is very sensitive to experimental conditions. Various modifications of the synthesis have been studied but with very limited success until the recent work by Bobbitt *et al.*[4] in which reduced amino acetals (e.g. **1**, R = H) having a C_3 oxygen substituent were shown to form 1,2,3,4-tetrahydroisoquinolines (**3**) when treated with 6N HCl and the solution subsequently hydrogenated.



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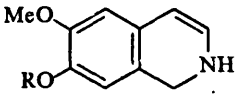

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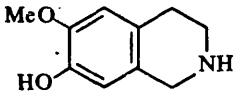

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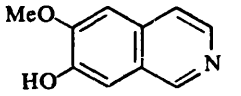

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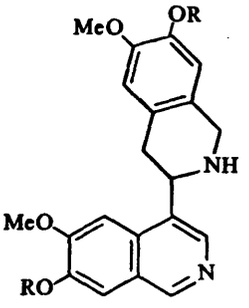
It was postulated[4] that a 1,2-dihydroisoquinoline (**2**, R = H) is an intermediate in the reductive cyclization, and although several attempts to isolate it were unsuccessful, support for this postulate was obtained by examining the products resulting from the treatment of the reduced aminoacetals of type (**1**, R = H) with 6N HCl *without* catalytic reduction. After 80 min at room temperature the 1,2,3,4-tetrahydroisoquinoline (**3**), the corresponding aromatic derivative (**4**), a dimer (**5**, R = H) and a trimer were isolated. Compounds **3** and **4** are the typical[5] products resulting from the disproportionation of a 1,2-dihydroisoquinoline in acid solution (although they

could be a function of the method of work-up used), and the dimer is most easily formulated[6] as an enamine reaction of a 1,2-dihydroisoquinoline. Further support for a 1,2-dihydroisoquinoline intermediate was provided by Bobbitt *et al.*[7] who showed that by boiling a solution of the reduced aminoacetal (**1**, R = H) with benzaldehyde and ethanolic HCl* for 30 min, a good yield of the 4-benzylisoquinoline (**6**, R = H) was obtained. A mechanism has been proposed by us[8] for this condensation reaction and some support for it is available by the isolation of intermediates such as **7** or **8**.



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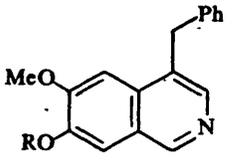

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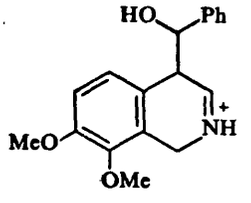
Bobbitt and Sih have now shown[9] that the treatment of reduced acetals such as **9** with 6N HCl at room temperature for 18 hr gives, not the 1,2-dihydroisoquinoline but the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**10**).



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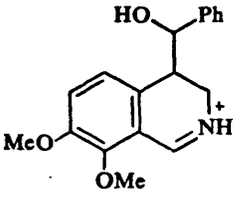

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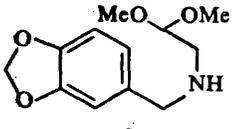

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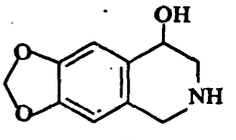

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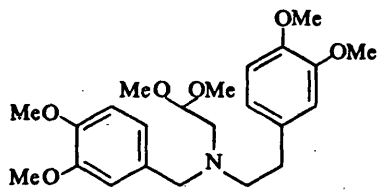
We have found by NMR studies that the aminoacetal derivative **11** is hydrolysed to the aldehyde **12** very rapidly by conc HCl, at room temperature, and that in a slower reaction[10] the doubly cyclized material **14** is formed in 80% yield. The aldehyde **12** was also prepared by Bobbitt's method using glycidol[11] and it also cyclized in good yield to **14**. The formation of **14** can be interpreted in terms of the initial formation of

* In all cases a 1:1 ethanolic concentrated hydrochloric acid solution was used.

the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (13) followed by nucleophilic attack at C_4 by the dimethoxyphenyl ring.

Bobbitt and Sih[9] seem to conclude that 1,2-dihydroisoquinolines are not involved in ANY of their previously described reactions of benzylaminoacetaldehyde dialkylacetals, but we suggest, however, that 1,2-dihydroisoquinolines are reactive intermediates in condensation reactions involving aldehydes. Thus, for example, benzaldehyde apparently fails to react with the tetrahydroalcohol (15) at RT (Experimental), whereas at higher temperatures, where dehydration of 15 to the corresponding 1,2-dihydroisoquinoline is rapid, condensation to form either 6 (R = CH_3) or 16 occurs.



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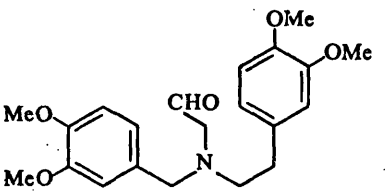

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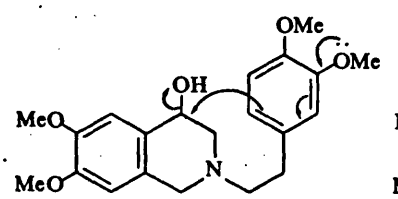

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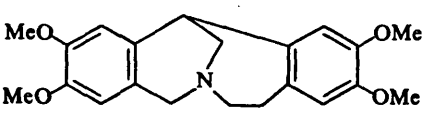

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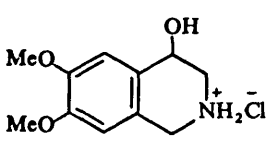
When a 1-benzyl-2-methyl-1,2-dihydroisoquinoline (17, R = Ar) is warmed with 2N HCl it rearranges[12,13] to the 2-methyl-3-benzyl-3,4-dihydroisoquinolinium salt (18, R = Ar), and we have recently shown[14] that 1-allyl-2-methyl-1,2-dihydroisoquinoline (17, R = —CH=CH_2) likewise rearranges to form 18 (R = —CH=CH_2). Although the mechanisms for benzyl and allyl migrations may not be identical,* each does involve a 1,2-dihydroisoquinoline as an intermediate. We have now found that when the aminoacetal (20, R = H), prepared[15] by the addition of allyl magnesium bromide to the Schiff's base (19), is warmed with ethanolic HCl the product, isolated in 80% yield, is the 3-allyl-3,4-dihydroisoquinolinium salt (21, R = H). The UV spectrum of the free base is typically that of a 3,4-dihydroisoquinoline (Experimental) and the NMR spectrum (in $CDCl_3$) is characteristic for the proposed structure; in particular the signal for the C_1 proton, at 8·2 ppm, appears as a doublet (J = 2 c/s)



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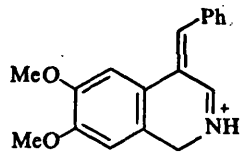

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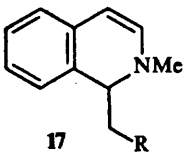
* The benzyl rearrangement may be viewed as a sigmatropic [1,3] migration, and as such is "forbidden"; the allyl migration, on the other hand, is an example of a suprafacial sigmatropic [3,3] reaction analogous to the Cope rearrangement, and may occur in a concerted manner under thermal conditions.



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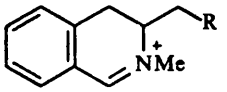

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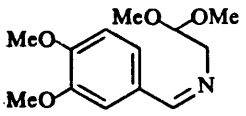

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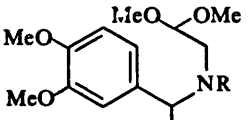

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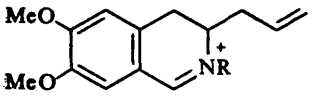
due to long range coupling with the methine proton at C_3. In the NMR spectrum of 6,7-dimethoxy-3,4-dihydroisoquinoline (**22**), in the same solvent, the C_1 proton appears as a triplet (J = 2 c/s) at 8·2 ppm and the two protons at C_3 form half of an A_2X_2 triplet at 3·7 ppm, further split (J = 2 c/s) into six lines. When the product **21** (R = H) was reacted with dimethyl sulphate and alkali a nitrogen-free *aldehyde* was obtained and characterized as its oxime. Structure **23** for this aldehyde is supported by its NMR spectrum which, in $CDCl_3$ solution, exhibits a 1 proton singlet at 10·3 ppm (—CHO); one hydrogen singlets at 7·4 and 6·95 ppm (C_2—H and C_5—H); one



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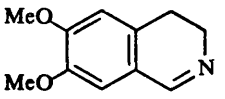

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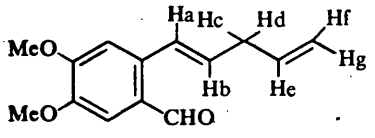


23

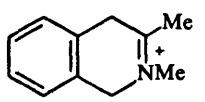
hydrogen doublet centred at 7·2 ppm (J = 15 c/s) (proton "a"); two hydrogen complex 6·4–5·7 ppm (protons "b" and "e"); two hydrogen complex 5·4–5·0 ppm (protons "f" and "g"); two three hydrogen singlets at 4·0 and 3·95 (2 × OCH_3) and a two hydrogen complex at 3·0 ppm (protons "c" and "d"). When the acetal **20** (R = Me), prepared by methylation of **20** (R = H) was treated with acids, the product, also isolated in 80% yield, proved to be **21** (R = Me); degradation with alkaline methyl sulphate produced the same aldehyde **23**. A 1-substituted -3,4-dihydroisoquinoline when degraded by this method[16] is converted into a ketone. The formation of **21** (R = H or Me) must surely involve the formation, from **20** (R = H or Me) of the 1-allyl-1,2-dihydroisoquinoline which then rearranges, and this reaction provides

very strong supporting evidence for the formation of 1,2-dihydroisoquinolines as intermediates in the cyclization and subsequent reactions of benzylaminoacetaldehyde dialkylacetals.

We have found that 2-methyl-1,2-dihydroisoquinoline (**24**) reacts in alcoholic hydrochloric acid solution with a variety of aldehydes to form 4-substituted-2-methylisoquinolinium salts (**25**); the results are summarised in Table 1, where yields are based upon 2-methyl-isoquinolinium iodide. The structures of the products follow from

24 **25**

their UV and diagnostic NMR spectra (Table 1A). but in addition the compound **25** (R = C_6H_5) was shown to be identical with authentic[17] 2-methyl-4-benzylisoquinolinium iodide. No identifiable isoquinoline derivatives were isolated when the enamine (**24**) was reacted with aliphatic aldehydes. We have also briefly examined the reaction of 2,3-dimethyl-1,2-dihydroisoquinoline with some aldehydes. In our preliminary experiments with this 1,2-dihydroisoquinoline the main product was the iminium salt (**26**), which is unusually stable; by a slight modification of procedure, however, the formation of this compound was suppressed. Under certain conditions a



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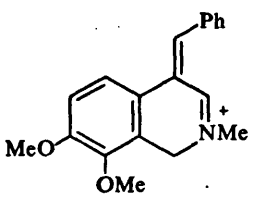

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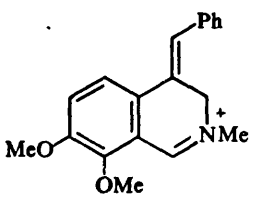

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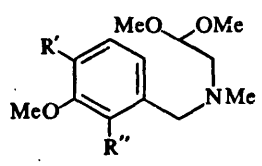
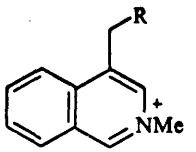
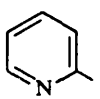


29

product, which may be formulated as **27** or **28**, can be isolated from the reaction of the acetal **29** (*R'* = H, R'' = OMe) and benzaldehyde. When attempts were made to recrystallize this compound a tautomeric change to the corresponding isoquinolinium salt (**30**) occurred, whereas reduction with sodium borohydride in aqueous ethanol gave the stilbene derivative (**31**), characterized as the methiodide.

TABLE 1 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS



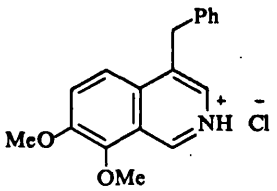
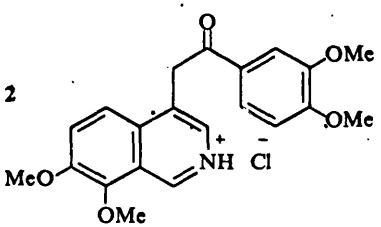
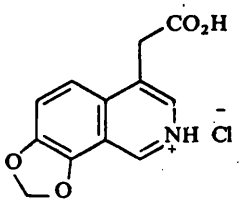
No.	R	% yield	m.p.	Molecular formula	Analysis								Solvent for recrystallization
					Required				Found				
					C	H	N	Cl	C	H	N	Cl	
1	C_6H_5—	38*	170–171°	$C_{17}H_{16}NO_4Cl$	61·15	4·8	4·2	—	61·2	4·75	4·4	—	EtOH
2	*p*-$MeOC_6H_4$—	39*	210–211°	$C_{18}H_{18}NO_5Cl$	58·4	5·0	3·8	—	58·8	5·0	3·8	—	EtOH
3	3,4-$(MeO)_2C_6H_3$—	20*	176–177°	$C_{19}H_{20}NO_6Cl$	58·0	5·2	3·6	—	58·4	5·2	3·8	—	EtOH
4	*p*-O_2N—C_6H_4—	39*	191–192°	$C_{17}H_{15}N_2O_6Cl$	53·9	4·0	7·4	—	53·9	3·8	7·6	—	EtOH
5	*o*-O_2N—C_6H_4—	46*	180–182°	$C_{17}H_{15}N_2O_6Cl$	53·9	4·0	7·4	9·4	54·2	3·7	7·2	9·5	EtOH
6	C_6H_5CO—	62*	185–186°	$C_{18}H_{16}NO_5Cl$	59·5	4·4	3·9	—	59·5	4·4	3·9	—	EtOH
7	CH_3CO—	27*	170–171°	$C_{13}H_{14}NO_5Cl$	52·2	4·7	4·7	—	52·2	4·9	4·7	—	EtOH
8	C_6H_5CH=CH—	33†	130–135°	$C_{19}H_{18}NCl$	77·2	6·1	4·7	—	67·3	6·3	5·1	—	aq. Acetone
9	2-Furfuryl	46*	269–270°	$C_{15}H_{14}NClO_5$	55·7	4·3	4·3	—	55·6	4·1	4·4	—	EtOH
10	3,4-Methylenedioxyphenyl	20†	126–128°	$C_{18}H_{16}NO_2Cl$	68·4	5·1	4·4	11·2	68·5	5·3	4·6	11·3	EtOH
11	—CO_2H	71*	191–192° (dec)	$C_{12}H_{12}NO_6Cl$	47·9	3·9	4·7	—	47·9	4·0	4·0	—	aq. Acetone
12		67·5*	224–225°	$C_{16}H_{15}N_2(ClO_4)_2$	44·2	3·7	6·6	—	44·3	3·9	6·5	—	MeOH

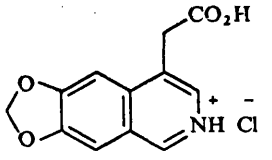
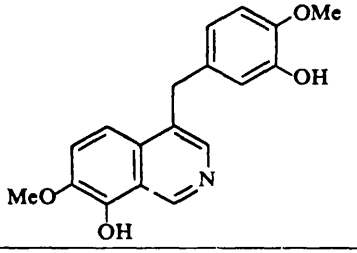
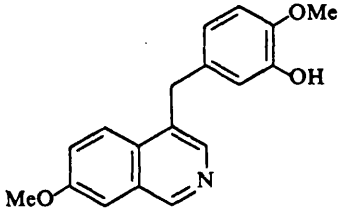
* As perchlorate. † As chloride.

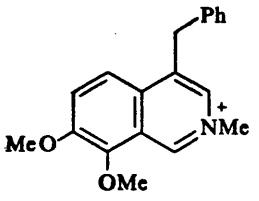
TABLE 1A. SPECTRAL DATA 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS

Compound No. (from Table 1)	Solvent	NMR ppm C_1—H	C_3—H	Aromatic protons C_4-Substituent	C_4—CH_2	$\equiv\overset{+}{N}CH_3$	Miscellaneous	UV λ_{max} (ε) mμ	IR $\bar{\nu}_{max}$ cm^{-1}
1	CF_3CO_2H	S 9·2	Complex ~7·9 [5]	S 6·1	S 4·45	S 4·35			1635, 1615
2	CF_3CO_2H	S 9·1	S 8·0	Complex ~7·85 [4] / AB quartet (J = 9·5 c/s, 7·1, 6·7	S 4·45	S 4·4	MeO—		1640, 1615
3	CF_3CO_2H	S 9·1	S 8·1	Complex ~7·9 [4] / Broad singlet [3] 6·75	S 4·45	S 4·3	2x MeO—		1635, 1610
4	CF_3CO_2H	S 9·35	Complex ~8·0 [5]	AB quartet (J = 8 c/s, 8·1, 7·3	S 4·7	S 4·6		232 (17,000) 270 (4130) 340 (2350)	1640, 1615
5	CF_3CO_2H	S 9·1	Complex 8·4 – 7·2 [9]		S 4·85	S 4·3			1635, 1615
6	CF_3CO_2H	S 9·2	S 8·2	Complex 8·3 – 7·3 [9]	S 5·0	S 4·4			1660, 1635, 1610, 1605
7	CD_3SOCD_3	S 9·6	S 8·3	Complex ~7·9 [4]	S 4·45	S 4·4	S 2·35 [3] CH_3—CO		1710, 1640, 1605
8	CF_3CO_2H	S 8·9	S 7·65	Complex 7·5 – 7·2 [11] aromatic and olefinic	Broad singlet 4·8	S 3·7		208 (19,400) 230 (14,700) 305 (9500)	1635, 1605
9	CF_3CO_2H	S 9·1	Complex ~8·0 [5]		S 4·45	S 4·3			1625, 1615
10	CF_3CO_2H	S 8·8	S 8·5	Complex 7·7 [4] / Broad singlet 7·15 [3]	S 5·2	S 3·95	S 6·0 [2] —O—CH_2—O—		1640, 1600
11	CF_3CO_2H	S 9·25	Complex ~8·1 [5]		S 4·45	S 4·5			1730, 1635 1600
12	CD_3SOCD_3	S 9·55	Complex 8·7 – 7·3 [9]		S 4·8	S 4·3			2800, 1635, 1610.

TABLE 2. MISCELLANEOUS 4-SUBSTITUTED ISOQUINOLINES FROM REDUCED AMINOACETALS

No.	Compound	% yield	m.p.	Molecular formula	Analysis								Solvent for Recrystallization
					Required				Found				
					C	H	N	Cl	C	H	N	Cl	
1		30	178–179°	$C_{18}H_{13}NO_2Cl$	68·4	5·7	4·4	11·2	68·5	5·4	4·7	11·8	EtOH
2		20	212–214°	$C_{21}H_{22}NO_5Cl$	62·3	5·5	3·5	—	62·2	5·6	3·6	—	EtOH
3		46	209° (dec)	$C_{12}H_{10}NO_4Cl$	53·9	3·8	5·2	—	54·1	3·7	5·5	—	2N HCl

4		68	274° (dec)	$C_{12}H_{10}NO_4Cl$	53·9	3·8	5·2	—	53·7	3·8	5·4	—	2N HCl
5		60	206–207°	$C_{18}H_{17}NO_4$	69·4	5·5	4·5	—	69·0	5·9	4·4	—	Ethylacetate
6		60	138°	$C_{18}H_{17}NO_3$	73·2	5·8	4·7	—	72·8	6·0	4·7	—	EtOH



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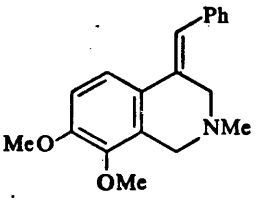
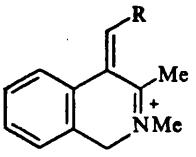


31

Similarly the products from the reaction of certain aromatic aldehydes (Experimental) with 2,3-dimethyl-1,2-dihydroisoquinoline were not the anticipated isoquinolinium salts, but rather of the type (**32**), in which one of the double bonds is exocyclic to the heterocycle. The NMR spectrum of these compounds, in trifluoroacetic acid, shows a one proton singlet at approx 8·0 ppm due to the H atom of the exocyclic double bond (the chemical shift of C_1—H of an isoquinolinium salt is normally ~9·2 ppm), a broad two proton singlet at 5·0–5·2 ppm, characteristic of a benzylic methylene function adjacent to a quaternary N atom (it is noteworthy that the chemical shift of the benzylic methylene protons of a 4-benzylisoquinolinium salt, in the same solvent, is 4·0–4·5 ppm) and a broad three proton singlet at 3·0 ppm, due to the Me group at C_3. The broadening of the signals associated with the Me and methylene groups presumably arises through long range coupling across 5 bonds,



32

a phenomenon observed in many heterocyclic systems.[18] Surprisingly, these compounds (e.g. **32**, R = Ph) are not readily isomerized to the corresponding isoquinolinium salts; this may in part be due to the hyperconjugative stabilization of the imminium system by the Me group at C_3.

Our results with 3,4-dimethoxybenzylaminoacetaldehyde dimethyl acetal (**1**, R = Me) are summarized in the Experimental. In some cases concomitant formation of N-alkylisoquinolinium salts and C_4-alkylated products was observed,[8] but under the conditions we now employ N-alkylation is only a very minor side reaction. Reaction between the aminoacetal (**1**, R = Me) and various *o*-nitrobenzaldehydes results in the formation of products which lack the methylene function at C_4 (as indicated by their NMR spectra) and the structures of these products, which are not yet assigned, are actively being examined. Similar products are obtained by the reaction of the same aldehydes with 2-methyl-1,2-dihydroisoquinoline in acid solution.

Into Table 2 have been collected the miscellaneous compounds prepared during the course of this work. Failure to achieve condensation between the aminoacetal (**1**, R = Me) and formaldehyde or butyraldehyde was observed, and the nitrogen

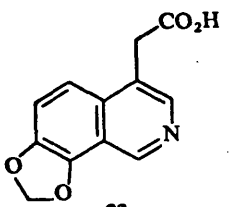
TABLE 2A. SPECTRAL DATA ON MISCELLANEOUS COMPOUNDS LISTED IN TABLE 2

Compound No. from Table 2	Solvent	NMR ppm							UV	IR
		C_1—H	C_3—H	Aromatic protons of isoquinoline nucleus	Aromatic protons of C-4 substituent	C_4—CH_2	OMe's	—OCH_2O—	λ_{max} (ε) mμ	$\bar{\nu}_{max}$ cm^{-1}
1*	$CDCl_3$*	S 9·5	S 8·25	AB quartet (J = 10 c/s) 7·5 (C_5—H), 7·15 (C_6—H)	S 7·05 [4]	S 4·2	S 3·95		236 (13,500), 255 (8360) 2801 (1650)	1630, 1605
2	CD_3SOCD_3	S 9·6	S 8·5	Complex 8·0–7·0 [7]		S 5·1	4·15 4·05 3·9 3·8		233 (40,500), 275 (14,400) 360 (3300)	1700, 1645, 1618
3	CF_3CO_2H	S 9·6	S 8·4	Singlet 7·99 [2] C_6—H, C_5—H)	—	S 4·45		S 6·5 (—OCH_2O—)	240 (23,720) 302 (2210) 379 (2480)	1700
4	CF_3CO_2H	Doublet 8·9 (J = 6 c/s)	Doublet 8·2 (J = 6 c/s)	Two singlets 7·45, 7·4 (C_8—H, C_5—H)	—	S 4·25	—	S 6·2 (—OCH_2O—)	246 (41,400)	1700
5	CD_3SOCD_3	S 9·5	S 8·3	Broad singlet 7·5 (C_6—H, C_5—H)	Complex 6·7	S 4·2	3·9 3·7			1640, 1610
6	CF_3CO_2H	Doublet 9·5 (J = 6 c/s)	Doublet 8·25 (J = 6 c/s)	AB quartet (J = 10 c/s) 8·35 (C_5—H), 7·9 (C_6—H)	Complex 7·0 [3]	4·5	4·15 4·0			*1630, 1600

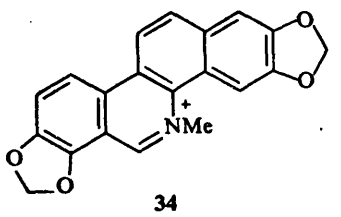
* As free base.

containing products resulting from the interaction of this acetal and acrolein, crotonaldehyde and salicylaldehyde resisted all attempts at characterization.

One of the most attractive features of this method for the preparation of 4-substituted isoquinolines in the relative ease with which 7,8-dioxygenated isoquinolines can be obtained, and we have used this approach to prepare **33**, which was required as a starting material for the first synthesis of the alkaloid sanguinarine (**34**).[19]



33



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EXPERIMENTAL

All m.ps are uncorrected. UV spectra were determined as EtOH solns and IR spectra as Nujol mulls. NMR spectra were recorded using a Varian A-60 spectrometer and chemical shifts are measured in ppm downfield from TMS as an internal standard.

N-[4-(3,4-Dimethoxyphenyl)butenyl]aminoacetaldehyde dimethylacetal (**20**, R = H).

N-(3,4-dimethoxybenzylidene)aminoacetaldehydedimethylacetal (25·3 g) was dissolved in dry ether (50 ml) and cooled to 0°, allyl magnesium bromide (0·17 mole) in ether (200 ml) was then added slowly, under a protective atmosphere of N_2. After stirring overnight at room temp, the reaction mixture was heated under reflux for a further 1 hr, and then cooled. 10% NH_4Cl aq (200 ml) was added to destroy the excess Grignard reagent; the aqueous phase was separated and washed with ether (2 × 100 ml). The combined ether extracts were dried and evaporated, to yield a pale yellow oil (24·5 g), distillation of which gave a fraction b.p. 140–144°/5 mm (23·8 g, 81%) of **20** (R = H). $\bar{\nu}_{max}$ cm^{-1}, 3340, 3080, 1645; NMR ($CDCl_3$) ppm, 7·0 s* [1] and 6·8 s [2] (aromatic protons); 5·6, 5·2, 5·0 complex [3] (—C<u>H</u>=C<u>H</u>$_2$); 4·4 tr [1], J = 6·5 c/s [—CH_2—C<u>H</u>$(OMe)_2$]; 3·9 s [6] (2 × —O<u>C</u>H_3); 3·6 tr, J = 7·75 c/s (Ar—C<u>H</u>—CH_2—); 3·2 s [6] (2 × —O<u>C</u>H_3); 2·6 d [2], J = 6·5 c/s (—C<u>H</u>$_2$—CH$(OMe)_2$); 2·4 d [2], J = 7·75 c/s (—C<u>H</u>$_2$—CH—Ar); 1·7 broad s [1], removed with D_2O (=N<u>H</u>). (Found: C, 65·3; H, 8·3; N, 4·7. $C_{16}H_{25}NO_4$ requires: C, 65·0; H, 8·5; N, 4·7%).

Methylation of this product with MeI (molar equiv) in acetone at room temp over Na_2CO_3 gave the corresponding **20** (R = Me); $\bar{\nu}_{max}$ cm^{-1}, 2800. (Found: C, 66·1; H, 8·1. $C_{17}H_{27}NO_4$ requires: 66·0; H, 8·0%).

Acid treatment of **20** (R=H). The secondary base (2·5 g) was dissolved in EtOH and conc HCl (1:1) and heated on a steam-bath for 3 hr, then set aside to cool. The following morning the soln was diluted with water (50 ml) and washed with ether (3 × 25 ml); basification of the aqueous phase with dil NH_4OH, followed by ether extraction gave, after evaporation of the solvent, a pink oil; $\bar{\nu}_{max}$ cm^{-1}, 1645, 1630; λ_{max} 234, 285, 316 (almost identical with the UV spectrum of 6,7-dimethoxy-3,4-dihydroisoquinoline) NMR ($CDCl_3$) ppm 8·2 d [1], J = 2 c/s (Ar—C<u>H</u>=N—CH(R²)—R); 6·8 s [1] (C_8—<u>H</u>); 6·7 s [1] (C_5—<u>H</u>); 5·8–4·1 complex [3] (C<u>H</u>$_2$—C<u>H</u>—); 3·9 broad peak [7] (2 × —O<u>C</u>H_3 and Ar CH_2—C<u>H</u>—CH_2—) ~2·5 complex (Ar C<u>H</u>$_2$—CH—C<u>H</u>$_2$—CH=CH_2). The NMR spectrum of **22** in $CDCl_3$ shows a 1H

* s = singlet; tr = triplet; d = doublet; m = multiplet.

triplet at 8·2 ppm J = 2 c/s and a pair of 2H triplets at 3 and 2·6, J = 7 c/s, the lower field triplet being further split into six lines, J = 2 c/s; this is indicative of the Ar—$\underline{CH}_2$—$\underline{CH}_2$—N=$\underline{CH}$— unit of structure. Reduction of this oil, which could not be distilled unchanged, with $NaBH_4$ in aqueous EtOH, afforded a gum, $\bar{\nu}_{max}$ cm^{-1}, 3320, 3075, 1645, from which a solid hydrochloride salt was prepared. Recrystallization from EtOH yielded pale yellow prisms m.p. 222–225°; $\bar{\nu}_{max}$ cm^{-1}, 3080, 2690, 2600, 2510, 2490, 1645; λ_{max} (ε) mμ 232 (7700), 285 (4400). (Found: C, 62·6; H, 7·5; N, 5·3; Cl, 12·9. $C_{14}H_{20}NO_2Cl$ requires: C, 62·3; H, 7·5; N, 5·2; Cl, 13·1%).

Acid treatment of **20**, R = Me). The tertiary base (3·09 g) in 6N HCl (25 ml) was diluted with EtOH (10 ml) and heated on a steam-bath for 3 hr and then allowed to cool overnight. After dilution with water (50 ml) the soln was washed with ether (3 × 50 ml) and neutralized by the addition of Na_2CO_3 aq. It was again washed with ether and treated with 10% KCNaq, which caused the separation of oily droplets. These were extracted into ether, and after removal of the solvent gave the pseudocyanide of **21** (R = Me) as colourless crystals (2·1 g, 78%), m.p. 68–70°; $\bar{\nu}_{max}$ cm^{-1}, 2815, 1645, 1610; λ_{max} (ε) mμ, 235 (8900), 286 (4200), 315 (2500), 372 (2100); NMR ($CDCl_3$) ppm s 6·75 [1] (C_8—$\underline{H}$), s 6·65 [1] (C_5—$\underline{H}$), complex 6·1–4·9 [3] (—$\underline{CH}$=$\underline{CH}_2$), s 4·7 [1] (C_1—$\underline{H}$), 3·9 s [6] (2 × —$O\underline{CH}_3$), 2·7 m (Ar $\underline{CH}_2$—$\underline{CH}$(—)—$\underline{CH}_2$—), s 2·6 [3] (=N$\underline{CH}_3$). (Found: C, 70·3; H, 7·4; N, 10·2. $C_{16}H_{20}N_2O_2$ requires: C, 70·6; H, 7·4; N, 10·3%).

Degradation of the rearranged product **21**, R = Me

Regeneration of the 3,4-dihydroisoquinolinium salt from the above pseudocyanide was not facile, being incomplete after heating under reflux with 2N HCl for 3 hr. Accordingly the above procedure was repeated up to the stage where the KCN soln was to be added, instead Me_2SO_4 (10 ml) and 2N NaOH (100 ml) were introduced. The reaction mixture was heated at 100° with stirring and, after 30 min, more Me_2SO_4 (5 × 2 ml) was added portionwise at 10 min intervals. After the last addition, and a further 30 min period of heating, the soln was cooled and extracted with ether (3 × 25 ml). The combined ethereal extracts were washed with 2N HCl (2 × 25 ml), dried and evaporated to give a greenish oil (0·98 g). TLC on SiO_2, developing the plate with benzene, AcOH, MeOH (45:4:8) solvent mixture, showed two components to be present, R_f 0·52 and R_f 0·33. The spot at R_f 0·52 being due to the major component. Column chromatography on SiO_2 eluting with $CHCl_3$ afforded a lemon coloured oil (0·9 g); $\bar{\nu}_{max}$ (ε) mμ 203 (11,400), 252 (21,200), 288 (9300), 323 (7000); NMR see page 6. (Found: C, 72·0; H, 6·8. $C_{14}H_{16}O_3$ requires: C, 72·4; H, 6·9%). This aldehyde (**23**) was converted into the corresponding oxime, a sticky solid, which was purified by chromatography on silica, $\bar{\nu}_{max}$ (ε) mμ, 249 (22,200), 285 (15,200). NMR ($CDCl_3$) ppm, 8·6 broad s [1], removed by deuteration (=N—$\underline{OH}$); 8·5 s [1] (Ar—$\underline{CH}$=NOH); singlet 7·3 [1] (C_8—$\underline{H}$); s 6·95 [1] (C_5—$\underline{H}$); d 6·65, J = 16 c/s [1] (Ar $\underline{CH}$=CH—); complex 6·25–5·6 [2] (=$\underline{CH}$—CH_2—$\underline{CH}$=); complex 5·3–4·9 [2] (—CH=$\underline{CH}_2$); s 3·9 [6] (2 × OCH_3); finely split tr 3·0 [2] J = 7 c/s (=CH—$\underline{CH}_2$—CH=). (Found: C, 68·7; H, 6·4; N, 5·0. $C_{14}H_{17}NO_3$ requires: C, 68·0; H, 6·9; N, 5·7%).

4-Benzyl-6,7-dimethoxyisoquinolinium chloride (**6**, R = Me). 3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (10·2 g) was dissolved with cooling in 1:1 conc HCl–EtOH (150 ml) and the soln allowed to stand at room temp for 20 hr. Benzaldehyde (5·1 g) was added and the reaction mixture heated upon a steam-bath for 30 min. Water was then added and the soln cooled to 0°. After 48 hr the orange red needles which had separated were collected, this material (6·3 g) melted at 192–195°. The mother-liquor was extracted with benzene, to remove unchanged benzaldehyde, and evaporated to yield a residue which, upon trituration with acetone, afforded an orange crystalline solid (3·0 g), m.p. 193–195°. The two crops of product were combined and recrystallized from MeOH to yield **16** as orange needles m.p. 193–195°; λ_{max} (ε) mμ, 211 (22,100), 280 (10,300), 300 (9700), 412 (4000); $\bar{\nu}_{max}$ cm^{-1} 2560, 1653, 1603; NMR (CF_3CO_2H) ppm 9·0 doublet [1], J = 8 c/s (C_1—$\underline{H}$), 8·5 s [1] (>C=$\underline{CH}$—Ph) 7·6 s [5] (aromatic protons); 7·5 s [1] (C_5—$\underline{H}$); 6·9 s [1] (C_8—$\underline{H}$); 5·2 s [2] (Ar—$\underline{CH}_2$—$\overset{+}{N}$<). This material was readily isomerized to the aromatic isoquinolinium salt by heating with MeOH under reflux for 1 hr; upon evaporation of the solvent to low volume and cooling, pale yellow cubes of **6** (R = Me) separated m.p. 194–196° (for analytical and spectroscopic data see Tables 1 and 1a).

6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinolinium chloride (**15**). A soln of 3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (20·4 g) in 6N HCl (400 ml) was allowed to stand at room temp for 17 hr. The solvent was carefully removed at 40° under reduced press to give an oily residue, trituration of which with acetone effected crystallization. The product (18·9 g) m.p. 177° (dec) was washed several times

with cold acetone–EtOH mixtures. (Found: C, 53·3; H, 6·6; N, 6·1; Cl, 15·1. $C_{11}H_{16}NO_3Cl$ requires: C, 53·8; H, 6·6; N, 5·7; Cl, 14·4%). Further recrystallization proved to be difficult.

Reaction of 6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinolinium chloride with benzaldehyde

A. 6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinolinium chloride (2·5 g) and benzaldehyde (1·26 g) were dissolved in 1:1 EtOH–conc HCl (25 ml) and the soln stirred at room temp for 72 hr, then diluted with water (25 ml) and cooled to 0° for 48 hr. Since after this time no product had separated, the unreacted benzaldehyde was recovered by extraction with benzene (6 × 10 ml); recovery 84%. In a control experiment 92% benzaldehyde was recovered from an identical procedure in which the addition of the tetrahydroisoquinolinium salt was omitted. Evaporation of the aqueous phase at 40° under reduced press gave a sticky residue (2·24 g) which crystallized on trituration with acetone to yield the unchanged tetrahydroisoquinolinium chloride (92%). After filtration, the acetone mother liquor, from which this compound was obtained, was evaporated to give a yellow oil (0·2 g), the NMR spectrum of which showed it not to be a 6,7-dimethoxy-4-benzylisoquinoline derivative (ratio of methoxyl to aromatic hydrogen atoms).

B. *Scale as above.* A soln of the tetrahydroisoquinolinium salt in ethanolic HCl was warmed on a steam-bath for 30 min, cooled to room temp and benzaldehyde added. This mixture was stored at room temp for 30 hr and then diluted with water. Unchanged benzaldehyde was removed by benzene extraction and the aqueous phase cooled to 0°. Later (48 hr) the orange crystalline product m.p. 193–195°, shown to be 4-benzylidene-6,7-dimethoxy 1,4-dihydroisoquinolinium chloride, was collected (0·26, 7·2%). The filtrate was basified with ammonia and then extracted first with ether (4 × 15 ml), then chloroform (4 × 15 ml). Evaporation of the combined ether extracts and crystallization of the residue from acetone afforded **5** (R = Me) as colourless prisms (0·26 g, 13·7%), m.p. 218–219°; λ_{max} mμ, 206, 248, 283, 312 and 327; $\bar{\nu}_{max}$ cm^{-1}, 1620, 1610. NMR ($CDCl_3$) ppm, 8·7 s [1] (C_1—H); 8·25 s [1] (C_3—H); 7·35 s [1] (C_8—H); 6·95 s [1] (C_5—H); 6·4 s [2] (C_5—H, C_8—H); 4·4 complex [1] (C_3—H); 4·1 s [2] (C_1—H_2); 3·95, 3·85 two s [3] (2 × OCH_3); 3·7 s [6] (2 × —OCH_3); 3·0 complex [2] (C_4—H_2); 2·0 broad s [1], removed by deuteration (=NH). (Found: C, 69·5; H, 6·4; N, 7·4. $C_{22}H_{24}N_2O_4$ requires: C, 69·5; H, 6·4; N, 7·4%). The hydrochloride salt of this dimer was also prepared white prisms m.p. 231–232°. (Found: C, 63·0; H, 6·0; N, 6·6. $C_{22}H_{25}N_2O_4Cl$ requires: C, 63·2; H, 6·05; N, 6·7%).

Removal of the solvent from the combined chloroform extracts yielded a small quantity of uncharacterized resinous material.

C. *Scale as in A above.* A soln of the tetrahydroisoquinolinium chloride in ethanolic HCl containing benzaldehyde was heated upon a steam-bath for 30 min. diluted with water and extracted with benzene (recovery of unreacted benzaldehyde 28%). After cooling at 0° for 48 hr the orange-red needles of 4-benzylidene-6,7-dimethoxy-1,4-dihydroisoquinolinium chloride (0·97 g, 31%), m.p. 192–195°, which had separated were collected, and the filtrate made basic with ammonia. Extraction with ether gave, after removal of the solvent, a gum which, when dissolved in benzene and saturated with HCl, yielded a crystalline ppt of **5** (R = Me) as the hydrochloride salt (0·4 g 17·7%). The filtrate from which this product separated was then evaporated to give 4-benzyl-6,7-dimethoxyisoquinolinium chloride (0·32 g, 10·1%). Extraction of the initial aqueous filtrate with chloroform afforded an uncharacterized resinous material (0·15 g).

2,3-Dimethyl-1,4-dihydroisoquinolinium perchlorate (**26**). 2,3-Dimethyl-1,2-dihydroisoquinoline (prepared by the LAH reduction of 10 g of 2,3-dimethylisoquinolinium iodide) in ether (100 ml) was treated with conc HCl (25 ml) in EtOH (50 ml). After heating at 100° for 1 hr the solvents were removed to yield a yellow oil, to which a little perchloric acid was added. Crystallization was initiated by scratching and cooling, thus yielding **26** as pale yellow prisms which were recrystallized from EtOH (1·5 g) m.p. 116–117°; ν_{max} cm^{-1}. 1695, 1090; NMR (CF_3CO_2H) ppm; 7·3 broad s [4] (aromatic protons), 5·0 broad s [2] (protons at C_1), 4·2 broad s [2] (protons at C_4) 3·8 s [3] ($\equiv\overset{+}{N}$—CH_3), 2·65 s [3] ($\equiv C_3$—CH_3). (Found: C, 50·8; H, 5·2; N, 5·35; Cl, 14·0. $C_{11}H_{14}NClO_4$ requires: C, 51·0; H, 5·0; N, 5·4; Cl, 13·7%).

This product was also obtained when aromatic aldehydes were introduced prior to heating, under reaction conditions similar to the above. In such cases little or no condensation products, formed by interaction of aldehyde and 1,2-dihydroisoquinoline, were isolated.

General reaction between 2,3-dimethyl-1,2-dihydroisoquinoline and aromatic aldehydes

The 1,2-dihydroisoquinoline, from LAH reduction of the corresponding isoquinolinium iodide (10 g) in ether, was freed of solvent by continuous pumping at 10 mm press for 2 hr, and the aldehyde (molar equiv, assuming total conversion of isoquinolinium salt to dihydroisoquinoline) in EtOH (50 ml) containing

conc HCl (25 ml) was then added. After heating under reflux for 4 hr, the solvent was removed under reduced press, and the residual oil treated with perchloric acid to give the crystalline perchlorate salt.

Benzaldehyde. 28% yield, m.p. 196–197° (aqueous EtOH), λ_{max} (ε) mμ, 232 (31,200), 350 (9000); $\bar{\nu}_{max}$ cm^{-1}, 1640, 1100; NMR (CF_3CO_2H) ppm, 7·9 singlet [1] (exocyclic olefinic proton), 7·3 complex [9] (aromatics), 5·0 broad s [2] (Ar—C$\underline{H}_2$—$\overset{+}{N}\equiv$), 3·9 s [3] ($\equiv\overset{+}{N}$—C$\underline{H}_3$), 2·9 broad s [3] (C_3—C$\underline{H}_3$). (Found: C, 62·0; H, 5·0; N, 4·1. $C_{18}H_{18}NO_4Cl$ requires: C, 62·2; H, 5·2; N, 4·0%).

p-Nitrobenzaldehyde, 65% yield, m.p. 256–257° (water), $^{N}_{max}$ (ε) mμ, 232 (31,200), 350 (9000); ν_{max} cm^{-1}, 1640, 1100; NMR (CF_3CO_2H) ppm 7·9 s [1] (exocyclic olefinic proton), 7·3 complex [9] (aromatics), 5·0 broad s [2] (Ar—C$\underline{H}_2$—$\overset{+}{N}\equiv$), 3·9 s [3] ($\equiv\overset{+}{N}$—C$\underline{H}_3$) 3·0 broad s [3] (C_3—C$\underline{H}_3$). (Found: C, 55·0; H, 4·3; N, 7·35; Cl, 9·3. $C_{18}H_{17}N_2ClO_6$ requires: C, 55·2; H, 4·1; N, 7·15; Cl, 9·1%).

m-Nitrobenzaldehyde. 43% yield, m.p. 243–246° (aqueous EtOH), λ_{max} (ε) mμ, 245 (39,150), 265 (4940), 350 (3120); NMR (CF_3CO_2H ppm 8·2 s [1] (exocyclic olefinic proton), 7·9 finely split s [1] (C_2—H), 7·5 complex [7] (aromatics), 5·2 broad s [2] (Ar—C$\underline{H}_2$—$\overset{+}{N}\equiv$), 3·9 s [3] ($=\overset{+}{N}$—C$\underline{H}_3$), 3·0 broad s [3] (C_3—C$\underline{H}_3$). (Found: C, 55·35; H, 4·25; N, 7·15; Cl, 9·25. $C_{18}H_{17}N_2ClO_6$ requires: C, 55·2; H, 4·1; N, 7·15; Cl, 9·1%).

p-Dimethylaminobenzaldehyde: 10% yield, m.p. 236–238° (EtOH), λ_{max} (ε) mμ, 240 (7420), 280 (8200), $\bar{\nu}_{max}$ cm^{-1}, 1649, 1090; NMR (CF_3CO_2H), 7·9 s [1] (exocyclic olefinic proton) ~7·5 complex [8] (aromatics), 5·2 broad s [2] (Ar—C$\underline{H}_2$—$\overset{+}{N}\equiv$), 4·0 s [3] ($\equiv\overset{+}{N}$—C$\underline{H}_3$), 3·4, 3·45 two s's [6] (—N(C$\underline{H}_3$)$_2$), 3·0 s [3] (C_3—C$\underline{H}_3$). (Found: C, 48·8; H, 5·2; N, 6·0: Cl, 14·8, $C_{20}H_{24}N_2Cl_2O_6$ requires: C, 48·9; H, 4·9; N, 5·7; Cl, 14·4%).

Reactions with veratrylaldehyde and glyoxalic acid failed to yield crystalline products.

4-Benzylidene-2-methyl-7,8-dimethoxy-1,4-dihydroisoquinolinium chloride (**27**).

The acetal **29** (R′ = H, R″ = OMe; 4·4 g) was dissolved in conc HCl (25 ml) and heated on a water-bath for 5 min. Benzaldehyde (1·7 g) was then added and the mixture heated for a further hr. After cooling at 0° for 48 hr, the orange crystalline product was collected, washed with conc HCl and EtOH and dried under vacuum. This material (3·5 g) m.p. 106–109° could not be recrystallized; ν_{max} cm^{-1}, 1650 ($\rangle C{=}\overset{+}{N}\langle$), 1608 ($\rangle C{=}C\langle$), λ_{max} (ε) mμ, 212 (22,000), 290 (17,100); NMR (CF_3CO_2H) ppm, 8·33 s [1] (C_3—H), 8·12 s [1] (exocyclic olefinic proton) 7·2 m [7] (aromatic protons), 5·0 s [2H] (Ar C$\underline{H}_2$—$\overset{+}{N}\equiv$). ~3·85 two s [6] (2 × OMe), 3·73 s [3] ($\equiv\overset{+}{N}$—CH_3).

Reduction of this product with $NaBH_4$ in aqueous EtOH gave a sticky solid, which with MeI afforded yellow prisms. Recrystallization of the latter from EtOH gave 4-benzylidene-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium methiodide, m.p. 241–242° (dec); $\bar{\nu}_{max}$ cm^{-1}, 1603 ($\rangle C{=}C\langle$); λ_{max} (ε) mμ, 223 (23,100), 312 (19,300); NMR (CF_3CO_2H) ppm, ~6·8 m [8] (aromatic and olefinic proton), 4·62 s [2] ($\equiv\overset{+}{N}$—C$\underline{H}_2$—), 4·37 s [2] (Ar—C$\underline{H}_2$—$\overset{+}{N}\equiv$), ~3·86 two s's [6] (2 × —OMe), 3·1 s [6] ($=\overset{+}{N}$(C$\underline{H}_3$)$_2$). (Found: C, 55·1; H, 5·5; N, 3·4. $C_{20}H_{24}NO_2I$ requires: C, 54·9; H, 5·5; N, 3·2%).

4-Benzyl-2-methyl-7,8-dimethoxyisoquinolinium perchlorate (**30**). The chloride **27** was dissolved in water and $HClO_4$ added to give the corresponding perchlorate salt (λ_{max} 209 and 286 mμ). Repeated recrystallization of this compound from EtOH gave **30** in 85% yield, as bright yellow needles m.p. 188–189°; $\bar{\nu}_{max}$ cm^{-1}, 1667 ($\rangle C{=}\overset{+}{N}\langle$), 1610 ($\rangle C{=}C\langle$). λ_{max} (ε) mμ, 219 (23,200), 258 (22,000). (Found: C, 57·6; 4, 5·2; N, 4·0. $C_{19}H_{20}NO_6Cl$ requires: C, 57·9; H, 5·1; N, 3·6%).

Reaction between 2-methyl-1,2-dihydroisoquinoline and aldehydes (Table 1)

2-Methyl-1,2-dihydroisoquinoline (0·01 mole) in ether (150 ml) was added to a soln of the aldehyde (0·01 mole) in EtOH (50 ml) and conc HCl (25 ml) protected by an atmosphere of N_2. After heating under reflux for 30 min, the soln was evaporated to yield a syrupy residue, which in the case of compounds numbered 8 and 10 (in Table 1) crystallized spontaneously; in the other examples the residue was treated with ethanolic perchloric acid to yield the crystalline perchlorate salt. Recrystallization was normally achieved from EtOH.

Reaction between 2-benzyl-1,2-dihydroisoquinoline and aldehydes

An identical procedure to that described above was carried out using 2-benzyl-1,2-dihydroisoquinoline,

prepared by the LAH reduction of 2-benzylisoquinolinium iodide. The products were characterized as the perchlorate salts.

p-Nitrobenzaldehyde. 4·0% yield, m.p. 180–181° (MeOH), λ_{max} (ε) mμ, 237 (31,620), 340 (5010); $\bar{\nu}_{max}$ cm^{-1} 1650, 1600; NMR (CD_3SOCD_3) 9·75 s [1] (C_1—H), 8·5 s [1] (C_3—H) ~7·5 complex [13] (aromatic protons) 5·6 s [2] (Ar—CH_2—$\overset{+}{N}\equiv$), 4·6 s [2] (—CH_2—Ar). (Found: C, 60·7; H, 3·9; N, 6·0. $C_{23}H_{19}N_2O_6Cl$ requires: C, 60·8; H, 4·2; N, 6·2%).

p-Methoxybenzaldehyde. 1·4% yield, m.p. 186–187° (EtOH), λ_{max} mμ, 240, 335, $\bar{\nu}_{max}$ cm^{-1}, 1650, 1615; NMR (CF_3CO_2H) ppm, 9·1 s [1] (C_1—H), 8·1–7·5 complex [5] (aromatic protons); 6·9 d [2], J = 9 c/s (C_2—H, C_6—H); 6·6 d [2], J = 9 c/s (C_3—H, C_5—H), 7·16 s [5] ($\equiv\overset{+}{N}$—CH_2—C_6H_5), 5·6 s [2] ($ArCH_2$—$\overset{+}{N}\equiv$): 4·4 s [2] (—CH_2—Ar); 3·8 s [3] (—OCH_3). (Found: C, 65·4; H, 4·9; N, 3·0. $C_{24}H_{22}NO_5Cl$ requires: C, 65·5; H, 5·0; N, 3·2%).

Reaction between the acetal (**1**, R = Me) *and aldehydes*

The reduced aminoacetal (5 g) in 6N HCl (30 ml) was stored at room temp for 12 hr; the aldehyde (5 g) was then added and the reaction mixture heated to 100° for 30 min (in the case of aldehydes which did not readily dissolve the minimum volume of EtOH necessary to effect soln was added). On cooling the hydrochloride salt normally separated slowly from the reaction medium, although in the case of *p*-methoxybenzaldehyde KI was added to precipitate the less soluble hydroiodide.

Benzaldehyde. 35% yield; m.p. 192–194° (water); λ_{max} (ε) mμ, 245 (6760), 313 (1000); $\bar{\nu}_{max}$ cm^{-1}, 1630, 1610; NMR (CF_3CO_2H) ppm, d 9·35, J = 5·5 c/s [1] (C_1—H); 8·25 d, J = 6 c/s [1] (C_3—H); 7·8 singlet [1] (C_8—H); 7·6 s [1] (C_5—H); 4·1, 4·05 two s's [6] (2 × —OCH_3) 4·55 s [2] (—CH_2Ar). (Found: C, 68·35; H, 5·8; N, 4·65. $C_{18}H_{18}NClO_2$ requires: C, 68·4; H, 5·7; N, 4·4%).

p-Methoxybenzaldehyde. 8% yield (as the hydroiodide), m.p. 188–189° (EtOH), λ_{max} (ε) mμ, 243 (12,200), 313 (5010); $\bar{\nu}_{max}$ cm^{-1}, 1630, 1610; NMR (CF_3CO_2H) ppm, 9·25 d, J = 6 c/s [1] (C_1—H); 8·35 d, J = 6 c/s [1] (C_3—H), 7·8 s [1] (C_8—H); 7·5 s [1] (C_5—H); 7·3 d, J = 10 c/s [2] (C_2—H, C_6—H); 7·1 d, J = 10 c/s [2] (C_3—H, C_5—H); 4·2, 4·1 two s's (2 × OCH_3). (Found: C, 52·6; H, 4·7; N, 3·2. $C_{19}H_{20}NIO_3$ requires: C, 52·3; H, 4·6; N, 3·2%).

p-Dimethylaminobenzaldehyde. 73% yield, m.p. 221–226° (aqueous MeOH), λ_{max} (ε) mμ 256 (64,100), 314 (10,500); $\bar{\nu}_{max}$ cm^{-1}, 1636, 1618; NMR (CF_3CO_2H) ppm, 9·4 d, J = 5·5 c/s [1] (C_1—H); 8·3 d, J = 6 c/s [1] (C_3—H); 8·0–7·6 complex [6] (aromatic protons); 4·15, 4·05 two s's [6] (2 × —OCH_3); 3·5, 3·55 two s's [6] (—$N(CH_3)_2$). (Found: C, 60·6; H, 6·1; N, 7·4; Cl, 18·1. $C_{20}H_{24}N_2Cl_2O_2$ requires: C, 60·8; H, 6·1; N, 7·1; Cl, 17·9%).

p-Nitrobenzaldehyde. Only a small amount of nitrogen containing compound was isolated for which satisfactory analyses were not obtained.

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FURTHER BERBINE SYNTHESES

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1,2-DIHYDROISOQUINOLINES—XI[1]

FURTHER BERBINE SYNTHESES[2]

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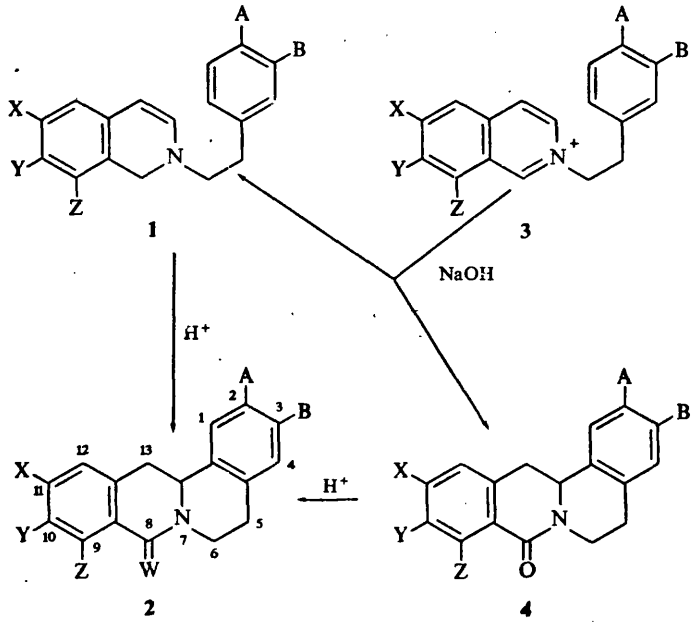
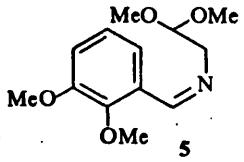
Abstract—New syntheses of tetrahydroberberine and tetrahydropalmatine are described and some other potential routes to the berbine skeleton are explored.

IN PART II of this series[3] we showed how the route to the berbine skeleton (**2**, W = H_2) involving[4,5] the cyclization of an N-β-arylethyl-1,2-dihydroisoquinoline (**1**) with acids could be simplified by generating the 1,2-dihydroisoquinoline by disproportionation of the parent isoquinolinium salt (**3**) with alkali. The isocarbostyril (**4**) also formed was found, unexpectedly, to cyclize to the 8-oxoberbine derivative (**2**, W = O). The majority of berberine and tetrahydroberberine alkaloids possess[6] a 2,3,9,10-tetra-oxygenation pattern whereas the above method of synthesis, which requires a pre-formed isoquinoline nucleus, gives rise most easily to a 2,3,10,11-tetraoxysubstitution pattern. 7,8-Dioxyisoquinolines were, until recently, very difficult to prepare, but by employing the modification of the Pomeranz–Fritsch[7] synthesis described by Bobbitt *et al.*,[8,9] 7,8-dioxy-1,2,3,4-tetrahydroisoquinolines (**8b**, R = H) are readily available. In this method a benzalaminoacetaldehyde dialkyl



acetal (5) is hydrogenated to **6**, dissolved in 6N HCl and the acid solution is hydrogenated again at room temperature. It was originally postulated that the reaction involves an acid-catalysed cyclization of **6** to the 1,2-dihydroisoquinoline **7**, which is then reduced to (**8b**, R = H), but it has now been shown[10] that the intermediate



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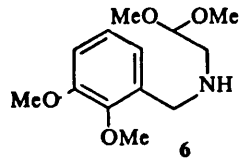

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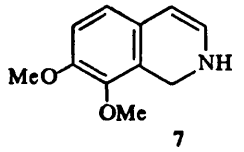

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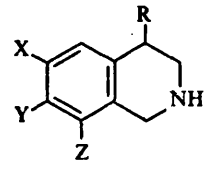
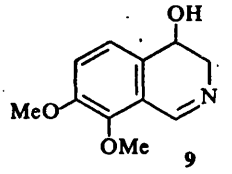


8a: X = Y = OMe; Z = H
8b: Y = Z = OMe; X = H



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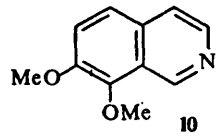

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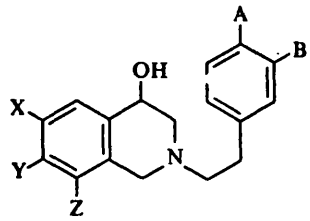
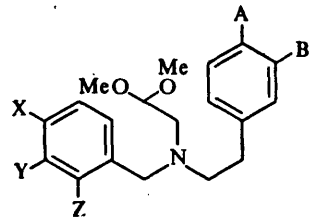
8b (R = OH) and not **7** is involved. Although in principle the tetrahydroisoquinoline **8b** (R = H) can be dehydrogenated to the fully aromatic structure **10** by standard methods, yields are very erratic, and a far superior method involves the treatment of **8b** (R = OH) with one mole of N-bromosuccinimide when an almost quantitative yield of the 3,4-dihydro-4-hydroxyisoquinoline **9** can be obtained; dehydration of this to the fully aromatic structure **10** is easily achieved in high yield by warming it with aqueous ethanolic HCl.

2-β-(3,4-Dimethoxyphenyl)ethyl-7,8-dimethoxyisoquinolinium bromide (**3**, A = B = Z = Y = OMe; X = H) was prepared either from **10** and β-3,4-dimethoxyphenylethyl bromide, or by reacting the 4-hydroxytetrahydroisoquinoline **11b** with N-bromosuccinimide; compound **11b** itself was prepared in high yield by



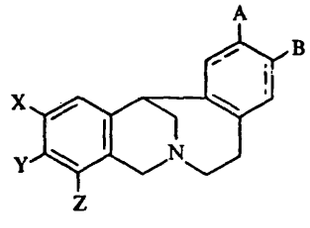
11a: X = Y = A = B = OMe; Z = H
11b: Y = Z = A = B = OMe; X = H

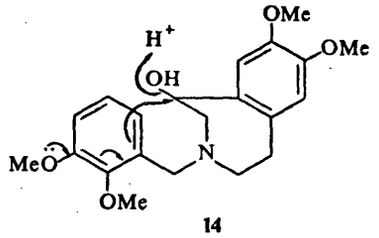


12a: X = Y = A = B = OMe; Z = H
12b: Y = Z = A = B = OMe; X = H

alkylation of **8b** (R = OH). Successive application of LAH and mineral acid as previously described[3–5] to the quaternary salt **3** gave tetrahydropalmatine (**2**, A = B = Y = Z = OMe; X = H; W = H_2) in 66% yield. Repetition of the sequence of reactions with **3** (X = H; Y = Z = OMe; A,B = —OCH_2O—) gave tetrahydroberberine in 58% yield, so that in principle a large number of the naturally occurring 2,3,9,10-tetraoxyberbines are accessible in a relatively simple manner. The full scope of this synthetic approach is now being studied.

Since the cyclization of benzylaminoacetals of type **6** involves the use of acid conditions, and since the cyclization of 2-β-arylethyl-1,2-dihydroisoquinolines of type **1** requires essentially similar conditions, it occurred to us[2] that the double cyclization of a suitably constituted benzylamino acetal, for example **12**, may be possible leading directly to a berbine derivative. When compound **12b** prepared from **6** and β-(3,4-dimethoxyphenyl)ethyl bromide was dissolved in conc HCl and the solution allowed to stand at room temperature for five days, a base hydrochloride $C_{21}H_{25}NO_4$ HCl could be isolated in 83% yield. The NMR spectrum of this material clearly indicates the presence of only FOUR aromatic protons, suggesting that a double cyclization had indeed occurred. The UV spectrum is benzenoid and there was no observable absorption in the IR in the 1600–1750 cm^{-1} region, but the product differs from an authentic sample of tetrahydropalmatine. It seemed possible that the first cyclization of **12b** had occurred to yield **11b** and that the second cyclization had occurred at C_4 of **11b** to yield **13b** and not at C_3 of a 1,2-dihydroisoquinoline to yield **2** (Y = Z = A = B = OMe; X = H; W = H_2). When the alcohol **11b**





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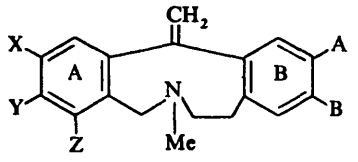
13a: X = Y = A = B = OMe, Z = H
13b: Y = Z = A = B = OMe; X = H
13c: X = H; Y = Z = OMe; A,B = OCH_2O
13d: X = A = B = OMe; Y = OH; Z = H

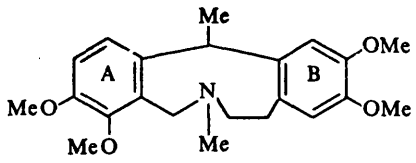
was treated with HCl under the conditions employed in the double cyclization of **12b** the product again was **13b** suggesting that the alternative initial cyclization of **12b** to **14**, followed by nucleophilic displacement of the OH group to yield **13b** is a less likely route for the reaction.

The structure **13b** is supported by the fact that Hofmann degradation yielded a methine base **15b** whose NMR spectrum (in $CDCl_3$) clearly supports the presence of the $\rangle C = CH_2$ group (a two proton quartet centred at 5·0 ppm). Further, when subjected to catalytic hydrogenation, one mole of gas was absorbed to yield a base whose NMR spectrum is devoid of absorption at 5·0 ppm but which exhibits instead

a three proton doublet (J = 7·5 Hz) at 1·7 ppm and a one proton quartet (J = 7·5 Hz) centred at 4·54, in agreement with the requirements for structure **16**. When compound **15b** was warmed with acetic acid a high yield of a quaternary salt was isolated (as the perchlorate) which is formulated as **17b**, the product of a transannular addition



15a: X = Y = A = B = OMe; Z = H
15b: Y = Z = A = B = OMe; X = H
15c: X = H, Y = Z = OMe; A,B = OCH_2O



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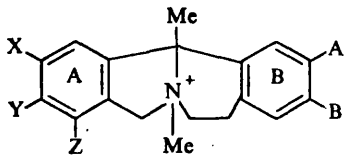

17a: X = Y = A = B = OMe; Z = H
17b: Y = Z = A = B = OMe; X = H

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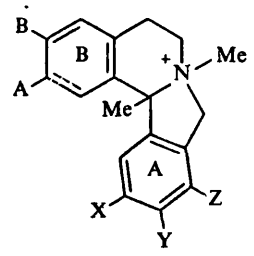
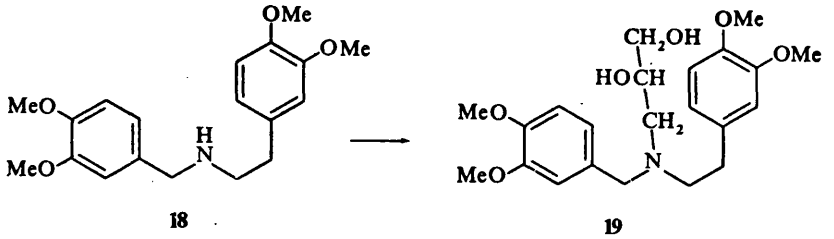


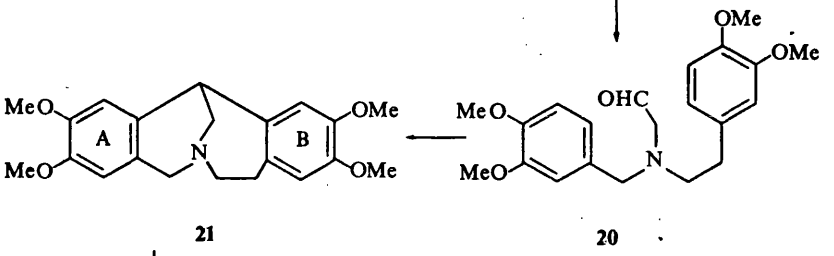
of the methylamino group to the exocyclic methylene group. The NMR spectrum of this material exhibits three proton singlets at 2·05 ppm (CH_3—$\overset{|}{\underset{|}{C}}$—) and at 3·25 ppm ($CH_3$—$\overset{+|}{\underset{|}{N}}$—), a two proton singlet at 4·9 ppm and clearly defined signals associated with four aromatic protons, four OMe groups and the A_2X_2 system of the $\diagdown\!\overset{+}{N}$—$CH_2$—$CH_2$—Ar fragment.

The cyclization of several differently substituted amino acetals of type **12** were studied under the standard conditions of conc HCl at room temperature for five days, but in each case cyclization occurred, not to the berbine skeleton, but to structures analogous to **13b**. The results are collected into Table 1. In all cases except No. 4 (which was methylated) Hofmann degradation yielded a methine analogous to **15b** and the conversion of No. 1 and No. 2 to **17b** and **17a** respectively was effected. The free amino aldehyde **20**, prepared as indicated in **18** → **20** was treated with conc HCl but again cyclization to **21** occurred, and not to the berbine.

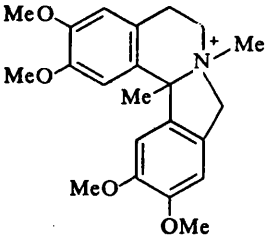
With the readily available dimethyl acetal **12a** a variety of conditions of acid treatment and temperature was studied in an effort to cause cyclization to occur to the berbine, but without success. In fact when a solution of the amino acetal in phosphoric acid was allowed to stand at room temperature for two days, the yield of **21** was raised to 90%. All attempts to synthesize the cyclized product **22** have so far failed.



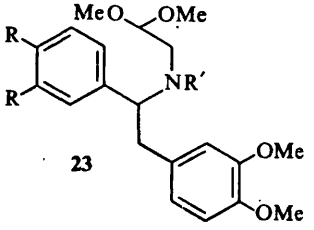
18 19



21 20



22 = 17a



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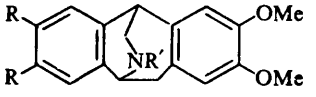

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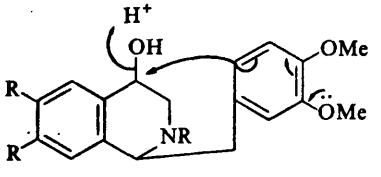

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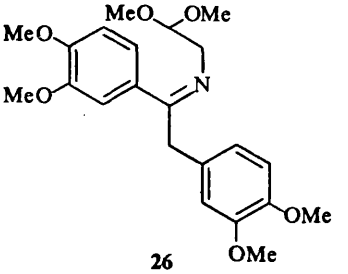

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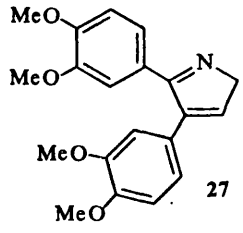
TABLE 1. CYCLIZATION OF THE BENZYLAMINOACETALDEHYDE DIMETHYLACETALS

Expt. No.	X	Y	Z	A	B	Yield %	m.p. HCl—	Molecular formula	Analysis Required C	H	N	Cl	Found C	H	N	Cl
1	H	OMe	OMe	OMe	OMe	83	225–6°	$C_{21}H_{26}NO_4Cl$	64·37	6·64	3·58	9·06	64·20	6·58	3·39	—
2	OMe	OMe	H	OMe	OMe	76	248–9°	$C_{21}H_{26}NO_4Cl$	64·37	6·54	3·58	9·06	64·09	6·82	3·54	8·80
3	H	OMe	OMe	O—CH_2—O		76	244–6°	$C_{20}H_{22}NO_4Cl$	63·92	5·86	3·73	9·45	63·73	6·12	3·95	9·20
4	OMe	OH	H	OMe	OMe	50	252–4°	$C_{20}H_{24}NO_4Cl$	63·57	6·36	3·69	4·39	63·62	6·62	3·46	8·99

An analogy for the observed double cyclization of the benzylamino acetals of type **12** is provided by the ring-closure of **23** (R = OMe; R′ = H) to give **24**(R = OMe; R′ = H) termed[13] isopavine. It is possible that this reaction proceeds by cyclization first to the 4-hydroxytetrahydroisoquinoline **25**, which then undergoes internal nucleophilic displacement of the OH group by the 3,4-dimethoxyphenyl ring. By treating **23** (R,R = OCH_2O; R′ = Me) with conc HCl we have been able to prepare a compound which has identical physical properties[14] to amurensinine **24** (R,R = OCH_2O; R′ = Me). Similarly the methiodide of **23** (R,R = OCH_2O; R′ = Me) gave a quaternary iodide which is identical with the methiodide of amurensinine. (We are indebted to Professor Santavy for the IR and NMR spectra of the alkaloid).

In 1903 Fritsch[15] reported that when the benzalamino-acetal **26** was treated with conc H_2SO_4 a base was obtained in 15% yield for which Guthrie *et al.*[12] proposed structure **27**. Although this was questioned by Battersby and Yeowell,[13] they did



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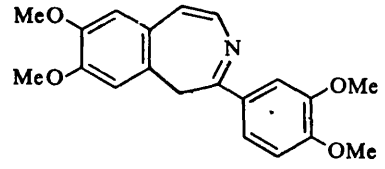

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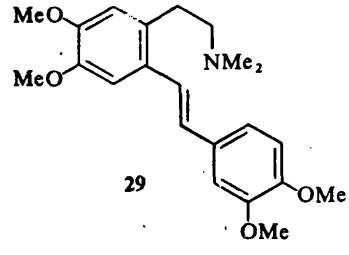
not make any alternative proposals. We have now found that the product described by Fritsch and by Guthrie *et al.* can be obtained in 37% yield merely by using conc HCl instead of conc H_2SO_4. The NMR spectrum of the base (Fig. 1) can be interpreted completely in terms of structure **28** and this deduction was confirmed by showing that the methine base **29** obtained from the tetrahydro derivative of **28** is identical with that produced from tetrahydropapaverine. Other unusual products have been



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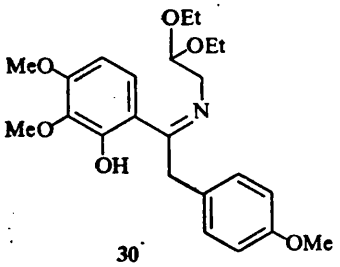
reported from time to time when benzalamino acetals were treated with acids. Thus, treatment of **30** with acids is reported[16] to yield a mixture of the expected isoquinoline and the novel structure **31**.

Another approach to the berbine skeleton was based upon the observation[17] that the isoquinoline Reissert[18] compound **32** when treated with perchloric acid yields a cyclic perchlorate **33**, which can be reduced by $NaBH_4$ or by catalytic



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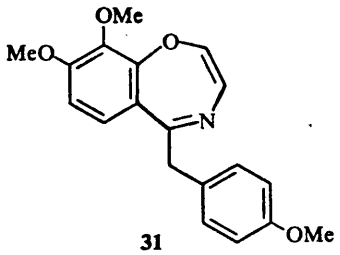

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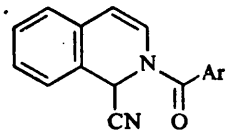

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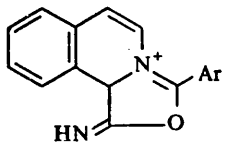


33

hydrogenation, to the 2-benzylisoquinaldamide **34** (A = B = C = W = X = Y = H), thus offering an improvement on the original[19] method. The amide **34** (A = B = C = W = H; X = Y = OMe) was easily prepared by this method and hydrolysed with 30% methanolic KOH to the carboxylic acid, which, with polyphosphoric acid

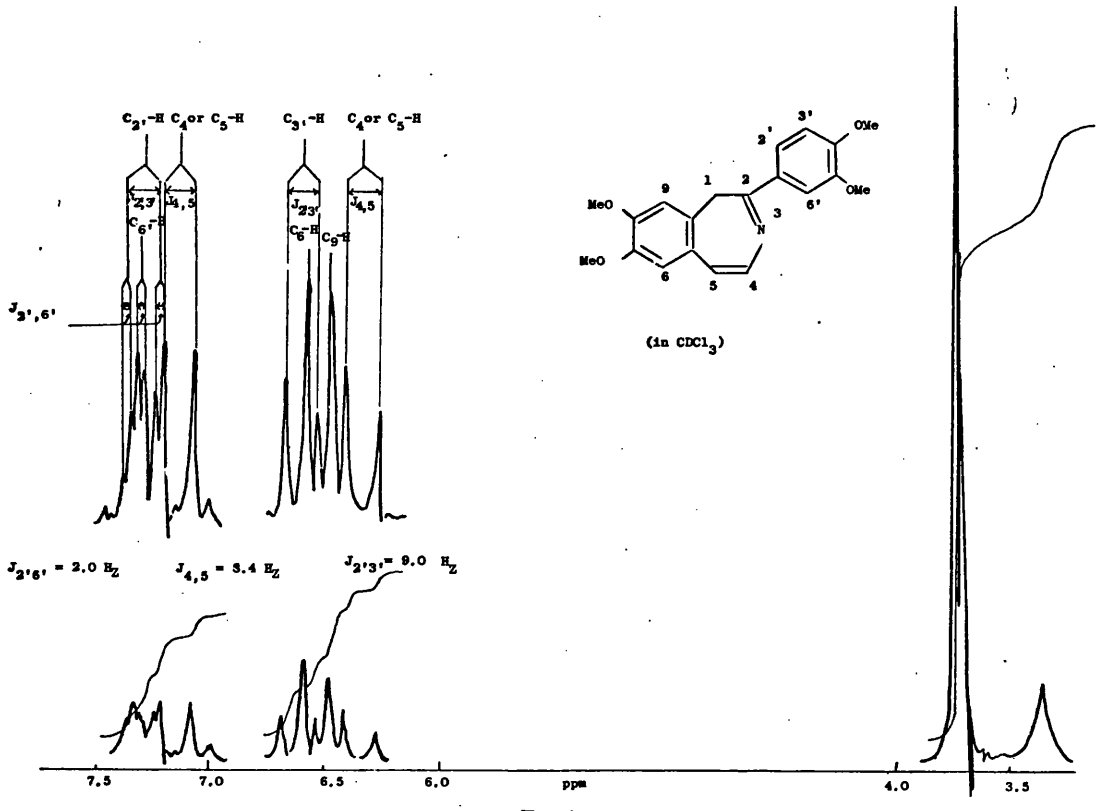
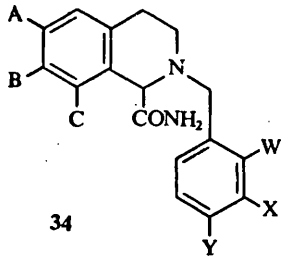


FIG. 1.

was converted into a weak base, isolated as the perchlorate. This substance, $C_{19}H_{18}NO_3\ HClO_4$ exhibited a UV absorption spectrum more complicated than that expected for a 13-oxoberbine, and one which is radically altered by the addition of base. The NMR spectrum contains signals associated with *seven* protons in the aromatic region; a band at 1690 cm^{-1} in the IR spectrum is consistent with the



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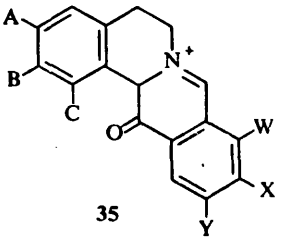

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absorption expected for an aromatic ketone and structure **35** (A = B = C = W = H; X = Y = OMe) was allotted to the substance.

With this route to the berbine skeleton established, an attempt was made to cyclize **34** (A = B = C = Y = H; W = X = OMe) but without success. Another attempt was made with the known[19] amide **34** (A = B = W = X = OMe; C = Y = H) which was reported[19] to be stable to boiling alkali and to acids. We were able, however, to hydrolyse this compound to the corresponding acid easily with 30% methanolic KOH, but all attempts to cyclize the acid have so far failed; decarboxylation has been observed instead with the formation of 2-(2,3-dimethoxybenzyl)6,7-dimethoxy-3,4-dihydroisoquinolinium salts.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**8a**, R = OH). N-3,4-Dimethoxylbenzyldimethylaminoacetal (5·0 g) was dissolved in 6N HCl (100 ml) and allowed to stand at room temp overnight. The soln was then cooled to 0° and basified with 30% NaOH aq; extraction with $CHCl_3$ and evaporation of the dried $CHCl_3$ extracts then afforded a pale yellow oil, which crystallized on exposure to acetone (2·9 g, 69%). Recrystallization from this solvent gave colourless solid m.p. 137–139° ν_{max} cm^{-1} 3240, 3170, 1610. (Found: C, 63·4; H, 7·6; N, 6·6. $C_{11}H_{15}NO_3$ requires: C, 63·1; H, 7·2; N, 6·7%).

7,8-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**8b**, R = OH), m.p. 140–141° (64%) was prepared in an analogous manner from N-2,3-dimethoxybenzyldimethylaminoacetal. (Found: C, 63·0; H, 7·2; N, 7·2. $C_{11}H_{15}NO_3$ requires: C, 63·1; H, 7·2; N, 6·7%).

2-β-(3,4-Dimethoxyphenyl)ethyl-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11a**). 6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (2·1 g) was treated with 3,4-dimethoxyphenethyl bromide (2·45 g) and Na_2CO_3 (1·0 g) in EtOH (15 ml) containing water (10 ml). The mixture was heated under reflux for 12 hr and the solvent then evaporated to yield semi solid which crystallized when triturated with acetone, yield 86%, m.p. 119–120° (from acetone) ν_{max} cm^{-1}, 3450, 1610, 1590. λ_{max} (ε) nm., 230 sh (9,060), 284 (3,100); NMR ($CDCl_3$) ppm, 6·75 singlet [3] (aromatic protons of phenethyl group); 6·9 singlet [1] (C_8—H); 6·5 singlet [1] (C_5—H); 4·5 triplet [1], J = 4Hz (—CH_2—CH—OH); 3·8 singlet [12] (4 × OCH_3); 3·6 singlet [2] (Ar—CH—N<); 3·4 singlet [1] (OH, lost on deuteration); 2·8 multiplet [6] ($ArCH_2CH_2N^+$< + —CH_2CHOH). (Found: C, 67·7; H, 7·2; N, 3·9; $C_{20}H_{27}NO_5$ requires: C, 67·5; H, 7·3; N, 3·8%). When treated with conc HCl at room temp in the course of 4 days this compound yielded 72% of a product shown to be **13a**.

2-β-(3,4-Dimethoxyphenyl)ethyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11b**) was prepared similarly as a colourless oil. Characterized as hydrochloride salt m.p. 206–207° (from aqueous EtOH),

ν_{max} cm^{-1}, 3320, 2620, 1610, 1590. (Found: C, 61·6; H, 6·8; N, 3·2; Cl, 8·6. $C_{20}H_{28}NO_5Cl$ requires: C, 61·6; H, 6·8; N, 3·4; Cl, 8·7%).

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6,7-*dimethoxyisoquinoline iodide* (3, X = Y = A = B = OMe, Z = H). The above 4-hydroxy-2-phenethyltetrahydroisoquinoline (1·0 g) in $CHCl_3$ (20 ml) was treated with small portions of NBS (total 0·48 g) during 15 min and the mixture then stirred for a further 3 hr. The brown soln was poured into a large volume of ether, and the solid which separated was then collected, dissolved in 6N HCl in EtOH (25 ml) and heated on a water-bath for 30 min. Evaporation yielded a dark residue which was taken up in hot-water and treated with KI, which caused a yellow crystalline solid to separate, yield 67%, m.p. 210–211° (lit.,[4] 209–210°) from aqueous MeOH. A mixed m.p. with an authentic specimen of 2-β-(3,4-dimethoxyphenyl)ethyl-6,7-dimethoxyisoquinoline iodide caused no depression.

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-7,8-*dimethoxyisoquinolinium iodide*, was prepared in an analogous manner from 2-β-(3,4-dimethoxyphenyl)ethyl-(4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline, yield 72%, m.p. 162–163, identical with a sample prepared by the quaternization of 7,8-dimethoxyisoquinoline with 3,4-dimethoxyphenylbromide followed by anion exchange (see below).

7,8-*Dimethoxyisoquinoline* (10). 7,8-Dimethoxy-4-hydroxytetrahydroisoquinoline (6·0 g) was treated with an equimolar quantity of NBS in a manner similar to that described in the preceding experiment. The residue, however, was not treated with aqueous KI soln but merely basified with NH_4OH to yield the free isoquinoline (3·85 g) in 71% yield as an oil, ν_{max} cm^{-1}, 1630, 1590, 1565; NMR (CF_3CO_2H) ppm, 9·8 doublet [1], J = 7Hz (C_1—H); 8·4 broad singlet [2] (C_3—H, C_4—H); 8·1 broad singlet [2] (C_5—H, C_6—H); 4·3, 4·2 two singlets [6] (2 × OCH_3). The free base was characterized as the perchlorate, bright yellow needles, m.p. 166–167° (from EtOH), ν_{max} cm^{-1}, 3260, 1640, 1605, 1590; λ_{max} (ε) nm., 236 (21,500), 252 (22,420), 290 sh (3,070), 360 (1,900). (Found: C, 45·5; H, 4·2; N, 4·8. $C_{11}H_{12}NO_6Cl$ requires: C, 45·6; H, 4·2; N, 4·8%).

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-7,8-*dimethoxyisoquinolinium iodide* (3, Y = Z = A = B = OMe; X = H). 7,8-Dimethoxyisoquinoline (0·9 g) and 3,4-dimethoxyphenethylbromide (1·25 g) in acetone (10 ml) were heated together for 20 hr, the solvent then removed and the residue triturated with ether. The crystalline bromide thus obtained was dissolved in water and KI added. The product a yellow solid recrystallized from EtOH/ether as needles, m.p. 162–163° (85%); ν_{max} cm^{-1}, 1635, 1610, 1570; λ_{max} (ε) nm., 258 (30,800), 287 sh (5530). The perchlorate salt was also prepared m.p. 164–165°. (Found: C, 55·5; H, 5·3; N, 3·15; Cl, 7·8. $C_{21}H_{24}NO_4Cl$ requires: C, 55·5; H, 5·3; N, 3·10; Cl, 7·8%).

± *Tetrahydropalmatine* (2, Y = Z = A = B = OMe; X = H, W = 2H). The above quaternary iodide (0·95 g) was suspended in THF (100 ml) and LAH (1·0 g) added in small portions. Stirring was continued for a total of 5 hr and the excess LAH then destroyed with 30% sodium potassium tartarate soln. The product 1,2-dihydroisoquinoline was extracted into CH_2Cl_2:ether (1:1) and the combined extracts evaporated to yield an oil (0·57 g); λ_{max} nm., 325. Without purification this oil was dissolved in conc HCl (10 ml) and allowed to stand at room temp for 5 days. After removal of the solvent the semi-solid residue was triturated with acetone affording a colourless solid which recrystallized from MeOH as needles. m.p. 210–212 (65·7%). The free base was liberated from this hydrochloride with ammonia, crystallizing as colourless prisms from EtOH m.p. 146–148° (lit.,[20] 147°); λ_{max} (ε) nm., 232 sh (16,800), 287 (4880), identical with an authentic specimen of ± tetrahydropalmatine. (Found: C, 71·7; H, 7·3; N, 4·1. Calc. for $C_{21}H_{25}NO_4$: C, 71·0; H, 7·1; N, 3·9%).

2-(3,4-*Methylenedioxyphenethyl*)7,8-*dimethoxyisoquinolinium iodide* (3, X = H; Y = Z = OMe; A,B = OCH_2O). This compound, golden needles m.p. 181–182° (from EtOH/ether), was prepared from the interaction of 3,4-methylenedioxyphenethyl bromide and 7,8-dimethoxyisoquinoline, followed by anion exchange, in 79·2% yield; ν_{max} cm^{-1}, 1630, 1600, 1560; λ_{max} (ε) nm., 258 (36,700), 293 (6690); NMR (CF_3CO_2H) ppm 9·25 singlet [1] (C_1—H); 8·25 singlet [2] (C_3—H, C_4—H); 8·05 singlet [2] (C_5—H, C_6—H); 6·8–6·5 multiplet [3] (aromatic protons of phenethyl substituent); 5·95 singlet [2] (OCH_2O); 5·0 triplet [2], J = 7·5 Hz ($ArCH_2CH_2\overset{+}{N}<$); 4·20 singlet [6] (2 × OCH_3); 3·35 triplet [2] ($ArCH_2$—$CH_2\overset{+}{N}<$). (Found: C, 51·8; H, 4·1; N, 3·2; I, 26·8. $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·0; I, 27·3%).

± *Canadine* (2, X = H; Y = Z = OMe; A,B = OCH_2O; W = 2H). The above iodide (0·61 g) was reduced to the corresponding 1,2-dihydroisoquinoline in the manner previously described, and the crude product treated with conc HCl (10 ml). After 5 days at room temp the soln was diluted, washed with benzene and evaporated. The residue crystallized upon trituration with EtOH, and the yellow product was then recrystallized from aqueous EtOH as prisms (58%) m.p. 160–162° (lit.,[24] 230–232°, this compound was not characterized however). (Found: C, 61·5; H, 6·4. $C_{20}H_{22}NO_4Cl$, H_2O requires: C, 61·0; H, 6·1%). The free base was liberated from the hydrochloride with NH_4OH and recrystallized from MeOH, giving white

prisms; λ_{max} (ε) nm., 230 sh (10,500), 292 (7520); m.p. 169–170° (lit.,[21] 170–171°). (Found: C, 71·0; H, 6·4; N, 4·3. Calc. for $C_{20}H_{21}NO_4$: C, 70·8; H, 6·2; N, 4·1%).

Preparation of N,N-*benzylphenylethylaminoacetals.* The benzylaminoacetal (0·1 m) in EtOH containing the appropriate β-arylethylbromide (0·01 m) was treated with Na_2CO_3 (1·0 g) and water (10 ml). After heating for 20 hr, under reflux, the EtOH was removed under reduced press and the oily base which had separated was extracted into ether. Removal of the ether gave the required dialkylated aminoacetals, in yields ranging from 92–95%, as pale yellow oils.

General cyclization procedure. The N,N-diakylaminoacetals (0·005 m) in conc HCl (10 ml) were allowed to stand at room temp for 5 days. The resultant red coloured solns were then washed with ether to remove non-basic material and evaporated to dryness. Trituration of the residues with acetone eventually afforded solid hydrochlorides which were recrystallized from EtOH. Yields, m.p. and analytical data for these salts are collected into Table 1. Compound **13b** was converted into the corresponding methiodide, m.p. 195–197°, which crystallized as colourless cubes from EtOH; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm., 240 sh (9650), 288 (5940); NMR (CF_3CO_2H) ppm, 6·8 singlet [2] (aryl protons ring A); 6·9 singlet [1] and 6·5 singlet [1] (aryl protons ring B); 4·8 triplet [1], J = 6 Hz (>C<u>H</u>—CH_2—$\overset{+}{N}$<); 4·0–2·8 multiplet [8] (aliphatic protons); 3·9 and 3·8 two singlets [12] (4 × —OC<u>H</u>$_3$); 3·4 singlet [3] (>$\overset{+}{N}$—C<u>H</u>$_3$). The methoperchlorate was also prepared, m.p. 240–242°, as colourlesss microcrystalline prisms from EtOH. (Found: C, 56·15; H, 6·0; N, 3·1. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; N, 3·0%).

Compound **13a**, [NMR ($CDCl_3$) 6·7, 6·5, 6·35, 6·3 singlets [4] (four aromatic protons); 3·8, 3·6 singlets [12] (4 × —OC<u>H</u>$_3$); 4·8–2·5 multiplets [10] (aliphatic protons)] was converted into the corresponding base, colourless prisms m.p. 154–155° (from EtOH) and thence to the methoperchlorate, deep yellow needles, m.p. 270–272° (EtOH). (Found: C, 56·2; H, 6·0; N, 3·2; Cl, 7·45. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; N, 3·0; Cl, 7·7%).

Compound **13c** was converted into the methiodide m.p. 274–275° and treated with perchloric acid to form the methoperchlorate, buff coloured prisms, m.p. 294–296°, from EtOH. (Found: C, 55·4; H, 5·4; H, 3·4; Cl, 7·5. $C_{21}H_{24}NO_8Cl$ requires: C, 55·6; H, 5·3; H, 3·1; Cl, 7·8%).

Compound **13d** when treated with MeI and Na_2CO_3 in acetone gave the same methiodide, m.p. 259–260° as obtained from **13a**, and addition of perchloric acid to this methiodide gave the identical methoperchlorate m.p. 270–272° (mixed m.p. and comparison of IR spectra) to that obtained in the above experiment.

General Hofmann degradative procedure. A suspension of the methiodide (or methoperchlorate) of the tetracyclic base (0·001 m) in 30% NaOH aq (25 ml) was heated under reflux for 3 hr, with constant stirring. On cooling the soln was extracted with ether (3 × 50 ml) and the dried combined extracts evaporated to yield the corresponding methine base.

Methine **15b** was obtained as an almost colourless resinous solid (75%) NMR ($CDCl_3$) ppm, 6·8 doublet [1], J = 8 Hz and 6·6 doublet [1], J = 8 Hz (aromatic protons ring A); 6·4 singlet [1] and 6·35 singlet [1] (aromatic protons ring B); 5·05 quartet [2], J = 2 Hz (>C=C<u>H</u>$_2$); ~3·7 two singlets [12] (4 × OC<u>H</u>$_3$); 3·4 singlet [2] (Ar C<u>H</u>$_2$—N<); 2·65 broad doublet [4] (>N—C<u>H</u>$_2$C<u>H</u>$_2$Ar); 2·15 singlet [3] (>N—C<u>H</u>$_3$). This compound was characterized as the methiodide, m.p. 213–215°, white prisms (acetone); ν_{max} cm^{-1}, 1600, 895; λ_{max} (ε) nm., 245 sh (10, 850), 294 (6650). (Found: C, 53·8; H, 6·1; N, 2·7; I, 24·8. $C_{23}H_{26}NO_4I$ requires: C, 54·0; H, 5·9; N, 2·7; I, 24·8%).

Methine **15a** recrystallized from EtOH as colourless prisms, m.p. 154–156°, 68%; ν_{max} cm^{-1}, 1605, 865 (>C=CH_2); λ_{max} (ε) nm., 245 sh (13,650), 290 (6820), NMR ($CDCl_3$) ppm 6·65 and 6·45 singlets [2] (protons ring A); 6·4 singlet [2] (protons ring B); 5·1 quartet [2], J = 2 Hz (>C=C<u>H</u>$_2$); ~3·7 three singlets [12H] (4 × OC<u>H</u>$_3$); 3·25 singlet [2] (Ar—C<u>H</u>$_2$—N<); 2·65 broad singlet [4H] (—C<u>H</u>$_2$—C<u>H</u>$_2$—); 2·15 singlet [3] (>N—C<u>H</u>$_3$). (Found: C, 71·6; H, 7·3; N, 3·8. $C_{22}H_{23}NO_4$. C, 71·5; H, 7·4; N, 3·8%).

Methine **15c** was obtained as a semi solid (52%); ν_{max} cm^{-1}, 1605, 1025, 860; λ_{max} nm., 245, 290 sh; NMR ($CDCl_3$) ppm, 6·8 doublet [1], J = 8 Hz and 6·5 doublet [1], J = 8 Hz (aromatic protons ring A); 6·4 singlet [2] aromatic protons ring B); 5·65 singlet [2] (—O—CH_2O—), 5·05 quartet [2], J = 2 Hz

(>C=CH$_2$); 3·7, 3·6 singlets [6] (2 × OCH$_3$); 3·4 singlet [2H] (ArCH$_2$—); ~2·7 multiplet [4H] (Ar—CH$_2$CH$_2$—N<); 2·15 singlets [3] (>N—CH$_3$). The methiodide of this methine crystallized from EtOH as cream coloured prisms, m.p. 224–226°; ν_{max} cm^{-1}, 1600, 1025, 880; λ_{max} (ε) nm., 247 sh (17,600), 302 (7730). (Found: C, 53·1; H, 5·5; N, 2·5; I, 25·9. $C_{22}H_{24}NO_4I$ requires: C, 53·3; H, 5·25; N, 2·8; I, 25·65%).

Reduction of methine base (**15b**). The base (0·4 g) was dissolved in 3N HCl (25 ml) and the soln hydrogenated over PtO_2 (50 mg) at room temp and atm press for 16 hr. The catalyst was then removed, and the soln made basic with NH_4OH and extracted with ether. Removal of the solvent from the combined extracts afforded the reduced **16** as a yellow oil (0·34 g), λ_{max} n.m., 285, which was characterized as the perchlorate salt. This latter compound, flesh coloured needles, m.p. 245–247°, crystallized from EtOH; λ_{max} (ε) 240 sh (4710), 285 (2190); NMR (CF_3COOH) ppm, 7·35 d [1], J = 9 Hz and 7·0 doublet [1], J = 9 Hz (aromatic protons ring A); 6·8, 6·6 two singlets [1] (aromatic protons ring B); 4·8–4·4 multiplet [3] (ArCH$_2$$\overset{+}{N}$< and >CH—CH$_3$); 3·8 broad based singlet [14] (4 × OCH$_3$ and Ar—CH$_2$—CH$_2$—$\overset{+}{N}$<); 3·1 multiplet [5] (>$\overset{+}{N}$—CH$_3$ and >$\overset{+}{N}$CH$_2$—CH$_2$—); 1·7 doublet [3], J = 7 Hz (>CH—CH$_3$). (Found: C, 56·2; H, 6·5; N, 3·5; Cl, 7·6. $C_{22}H_{39}NO_8Cl$ requires: C, 56·0; H, 6·4; N, 3·0; Cl, 7·5%).

Transannular cyclization of the methine bases. A soln of the methine base (0·001 m) in glacial AcOH (25 ml) was allowed to stand overnight at room temp. Evaporation of the solvent gave a gummy residue which dissolved in 2N HCl (10 ml) and the soln washed with ether (2 × 10 ml), basified with NH_4OH and extracted with CH_2Cl_2 (3 × 10 ml). Removal of the solvent from the dry combined extracts yielded a resinous solid, which when dissolved in EtOH (10 ml) and a few drops of perchloric acid added crystallized as the corresponding perchlorate salt.

The perchlorate salt **17b** obtained in 39·6% yield, recrystallized from a large volume of EtOH as colourless needles, m.p. 254–255°; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm., 240 sh (10,200), 290 (5480); NMR (CF_3CO_2H) ppm, 6·95 singlet [3] and 6·7 singlet [1] (aromatic protons); 4·8 singlet [2] (Ar CH$_2$—$\overset{+}{N}$<); ~3·9 broad based singlet [14] (4 × OCH$_3$ and —CH$_2$CH$_2$Ar); ~3·3 broad singlet [5] (>$\overset{+}{N}$—CH$_3$ and >$\overset{+}{N}$—CH$_2$CH$_2$—); 2·15 singlet [3] (>C—CH$_3$). (Found: C, 56·0; H, 6·4; Cl, 7·3. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; Cl, 7·7%).

N-3,4-Dimethoxybenzyl-N-3,4-dimethoxyphenylethylaminoacetaldehyde (**20**). The amine **18** and an equimolar amount of glycidol were heated on a water-bath for 2 hr, the mixture was then diluted with $CHCl_3$ and water and cooled to 0°. Sodium metaperiodate (0·01M) in water was then added dropwise with vigorous agitation during 15 min. The two phase soln was then made basic (pH 8) with N NaOH and further stirred for 3 hr. The $CHCl_3$ layer was then removed and evaporated to give an orange-yellow oil (80%), ν_{max} cm^{-1}, 1730, which was not purified but used directly in cyclization experiments under conditions previously described for the corresponding dimethylacetal, the product **21** was identical in all respects with that obtained from the aminoacetal (No. 2 in Table 1).

Benzylaminoacetal (**23**, R = R = OCH_2O; R′ = Me). 3,4-Dimethoxylbenzyl-3,4-methylenedioxyphenyl ketone (1·5 g) and aminoacetal (2·0 g) were heated together at reflux temp for 3 hr during which time excess aminoacetal was slowly allowed to distill. The residual oil was dissolved in EtOH (50 ml) and hydrogenated at 2 atm press over PtO_2 (0·5 g) during 5 hr. The benzylaminoacetal was then converted directly into its N-Me derivative by the addition to the above soln of glacial AcOH (0·5 ml), 37% aqueous formalin (0·5 ml) and continuation of the hydrogenation for a further 4 hr. Removal of the catalyst and solvent gave an oil which was dissolved in ice cold 2N H_2SO_4 and washed with ether. The purified product was liberated from the acid phase with NH_2OH and extracted into CH_2Cl_2. After evaporation of the solvent from these latter extracts the product (1·8 g) was obtained as a yellow oil; ν_{max} cm^{-1}, 1610, 1590.

Amurensinine (**24**, R,R = OCH_2O, R′ = Me). Without further purification the oil was cyclized in the usual manner, basification of the acid soln produced a brown oil which was purified by chromatography upon an alumina column. Elution with benzene:pet ether (1:1) yielded amurensine (0·36 g), 24%. m.p. 158–160° (lit.[14], 160–164°); λ_{max} nm, 233 sh, 253, 296, ν_{max} cm^{-1}, 1606. The methiodide was obtained as

colourless prisms, m.p. 266–268° (lit,[14] 273–275°), from MeOH/ether; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm, 233 sh (12,700), 253 sh (4020), 296 (6680); NMR (CF_3CO_2H) ppm 7·05, 6·95, 6·90, 6·80 four singlets [4] (aromatic protons); 6·05 quartet [2], J = 2 Hz (OCH_2O); 4·8 triplet [1], J = 6 Hz, (C<u>H</u>—CH_2), 3·9–4·1 multiplet [3] (aliphatic protons); 4·0, 3·9 two singlets (2 × OMe); 3·58, 3·20, two singlets [6] (2 × $\overset{+}{N}CH_3$). (Found: C, 52·0; H, 5·2; N, 2·7; I, 26·6. Calc. for $C_{21}H_{24}NO_4I$, C, 52·4; H, 5·2; N, 2·9; I, 26·4%).

The Fritsch product (**28**). The compound was obtained as previously described by Guthrie *et al.*,[12] and recrystallized from EtOH as yellow needles, m.p. 161–162° (lit.,[12] 164–165°); ν_{max} cm^{-1}, 1590 (>C=N—), 1565 (>C=C<); λ_{max} (ε) nm, 228 (22,100), 261 (13,100), 318 sh (7360), 346 (8470), NMR, see Fig. 1. By using conc HCl at RT during 24 hr the yield of **28**, as the hydrochloride, was increased to 37%.

Reduction of the Fritsch product. Hydrogenation of the above base (0·4 g) in EtOH (100 ml) over Adams catalyst (0·05 g) at 2 atm press afforded a colourless oil (0·4 g) which was characterized as the hydrochloride; colourless solid m.p. 230–232° (from EtOH/ether) ν_{max} cm^{-1}, 2750, 2650, 2440, 1610. The methiodide was isolated as colourless nodules m.p. 179–180°, from MeOH–ether, containing 1 mol MeOH of crystallization; ν_{max} cm^{-1}, 3350–3450, 1610; λ_{max} (ε) nm, 236 sh (18,100), 283 (7960). (Found: C, 51·4; H, 6·35; N, 2·4; I, 24·5. $C_{22}H_{30}NO_4I$ requires: C, 51·9; H, 6·40; N, 2·6; I, 24·0%).

Formation of the methine (**29**). The above methiodide (0·3 g) was heated under reflux with 30% NaOH aq (20 ml) for 3 hr. After cooling the soln was extracted with ether and the combined extracts evaporated to yield a colourless oil. This was dissolved in ether and the soln saturated with gaseous HCl, causing the corresponding hydrochloride to separate as a colourless solid, which recrystallized from aqueous EtOH, m.p. 218–220 (lit.,[23] 220–221°), yield 90%. This product was converted into the perchlorate salt, m.p. 206–208° (from EtOH), λ_{max} (ε) nm, 296 sh (15,700), 331 (22,300). This UV spectrum is identical with that reported by Knabe.[22] (Found: C, 55·95; H, 6·3; N, 3·2; Cl, 7·4. $C_{22}H_{30}NO_8Cl$ requires: C, 56·0; H, 6·4; N, 3·0; Cl, 7·5%).

2-(3,4-*Dimethoxylbenzoyl*)1,2-*dihydroisoquinaldonitrile.* Isoquinoline (12 g) in CH_2Cl_2 (70 ml), KCN (30 g) in water (300 ml) and veratroyl chloride [from veratric acid (22 g)] were shaken vigorously together for 5 min. The solid product (11·5 g) was filtered off washed with water and EtOH; addition of EtOH to the filtrate afforded a further crop of crystalline product (4·5 g). The combined crops were recrystallized from EtOH to yield 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile as very small colourless prisms (16 g), m.p. 213–215°. λ_{max} (ε) nm, 228 (25,800), 296 (15,100). ν_{max} cm^{-1}, 1660, 1640. (Found: C, 71·5; H, 5·15; N, 8·85. $C_{19}H_{16}N_2O_3$ requires: C, 71·25; H, 5·05; N, 8·75%).

2-(2,3-*Dimethoxybenzoyl*)1,2-*dihydroisoquinaldonitrile.* This compound was prepared in an identical procedure to that described above from 2,3-dimethoxybenzoyl chloride. Recrystallization from EtOH gave colourless prisms (12 g), m.p. 132–134°; λ_{max} (ε) nm, 228 (26,700), 290 (15,500); ν_{max} cm^{-1}, 1680, 1640. (Found: C, 71·1; H, 5·15; N, 8·9. $C_{19}H_{16}N_2O_3$ requires: C, 71·25; H, 5·05; N, 8·75%).

2-(2,3-*Dimethoxybenzoyl*)6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinaldonitrile.* As above, using 6,7-dimethoxy-3,4-dihydroisoquinoline (12·0 g) and 2,3-dimethoxybenzoylchloride (15 g). The product was recrystallized from EtOH; yield (6 g), m.p. 163–165°; ν_{max} cm^{-1}, 1650. (Found: C, 65·5; H, 5·65; N, 7·2. $C_{21}H_{22}N_2O_5$ requires: C, 65·9; H, 5·8; N, 7·35%).

Preparation of perchlorate salts. 2-(3,4-Dimethoxybenzoyl)1,2-dihydroisoquinaldonitrile was treated with glacial AcOH, a little 60% perchloric acid added and the yellow soln thus obtained was warmed for 20 min upon a water-bath. On cooling an almost quantitative yield of the perchlorate salt was obtained, which recrystallized from a large volume of EtOH as yellow needles, m.p. 205–206°, ν_{max} cm^{-1}, 3400–3180, 1670, 1640. (Found: C, 54·2; H, 4·9; N, 6·35; Cl, 8·4. $C_{19}H_{16}N_2O_3$, $HClO_4$ requires: C, 53·9; H, 4·95; N, 6·60; Cl, 8·35%).

The perchlorates of 2-(2,3-dimethoxybenzyl)1,2-dihydroisoquinaldonitrile and 2-(2,3-dimethoxylbenzyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile were similarly prepared as yellow needles, m.p. 186–189°. (Found: C, 53·85; H, 4·95; N, 6·65; Cl, 8·45. $C_{19}H_{16}N_2O_3$, $HClO_4$ requires: C, 53·7; H, 4·95; N, 6·6; Cl, 8·35%), and m.p. 236°. (Found: C, 51·8; H, 5·05; N, 5·8; Cl, 7·65. $C_{21}H_{22}N_2O_5$, $HClO_4$ requires: C, 52·2; H, 4·8; N, 5·8; Cl, 7·35%) respectively.

2-(3,4-*Dimethoxybenzyl*)1,2,3,4-*tetrahydroisoquinaldamide* (**34**, A = B = C = W = H; X = Y = OMe). 2-(3,4-Dimethoxylbenzoyl)1,2-dihydroisoquinaldonitrile perchlorate (14 g) in 50% aqueous EtOH (240 ml) was heated on a water-bath and $NaBH_4$ (4 g) added in small portions over 20 min. After a further 30 min the volume of the soln was decreased to about 140 ml and allowed to cool. The colourless crystalline product was recrystallized from EtOH as long needles (4·6 g) m.p. 179°. ν_{max} cm^{-1}, 3450, 3320, 1670, 1630. (Found:

C, 69·55; H, 6·75; N, 8·55. $C_{19}H_{22}N_2O_3$ requires: C, 69·9; H, 6·8; N, 8·6%). This compound was characterized as the perchlorate salt, colourless prisms from EtOH, m.p. 209–210°. (Found: C, 53·45; H, 5·2; N, 6·6; Cl, 8·55. $C_{19}H_{22}N_2O_5$, $HClO_4$ requires: C, 53·45; H, 5·45; N, 6·55; Cl, 8·3%).

2-(2,3-Dimethoxybenzyl)1,2,3,4-tetrahydroisoquinaldamide (34, A = B = C = Y = H; W = X = OMe). This was obtained in an identical manner to that described above as a yellow oil (14 g), characterized as the perchlorate, colourless prisms m.p. 204·5–205° from EtOH. (Found: C, 53·65; H, 5·15; N, 6·7; Cl, 8·6. $C_{19}H_{22}N_2O_3$, $HClO_4$ requires: C, 53·45; H, 5·45; N, 6·55; Cl, 8·5%).

2-(3,4-Dimethoxybenzyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldamide (34, A = B = X = Y = OMe; C = W = H). In a similar experiment 2-(3,4-dimethoxybenzoyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile perchlorate (2·7 g) was reduced to give the corresponding aldamide (0·3 g) as long colourless needles m.p. 189–192° (lit., 191°) from aqueous EtOH. Attempts to prepare the perchlorate salt failed.

2-(3,4-Dimethoxybenzyl)1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid. 2-(3,4-Dimethoxylbenzyl)1,2,-3,4-tetrahydroisoquinaldamide (7 g) in conc HCl (80 ml) was heated at reflux for 1 hr and then cooled. Some resinous material was removed and the soln made alkaline with 30% NaOH aq and made just acid with AcOH; after filtration through Kieselguhr the soln was extracted with CH_2Cl_2 (4 × 60 ml) and the combined extracts were then dried and evaporated to give the corresponding acid; which recrystallized as long, colourless needles (2·0 g), m.p. 164–165°, from EtOH. (Found: C, 67·3; H, 6·8; N, 4·65. $C_{19}H_{21}NO_4\frac{1}{2}H_2O$ requires: C, 67·87; H, 6·6; N, 4·15%). This acid was also prepared from the amide (9·0 g) by heating at reflux with 30% ethanolic KOH (100 ml) for 24 hr, yield 5·6 g.

2-(2,3-Dimethoxybenzyl)1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylic acid. 2-(2,3-Dimethoxybenzyl)1,2,3,4-tetrahydro 6,7-dimethoxyisoquinaldamide (0·4 g) was heated under reflux with 30% ethanolic KOH (10 ml) for 24 hr, some EtOH was then distilled and water (10 ml) added. After filtration the soln was extracted with CH_2Cl_2 (4 × 20 ml) and the combined extracts evaporated to yield the acid as an oil, which crystallized, on trituration with EtOH, as small prisms m.p. 183–185°, ν_{max} cm^{-1} 3100–3200, 1620. This material was not further purified, but used directly in subsequent experiments.

2-(2,3-Dimethoxylbenzyl)1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid. This compound was obtained from the corresponding amide (16 g) by hydrolysis with conc HCl (100 ml) as described above. Addition of EtOH to the oily product (3·5 g) did not effect crystallization; the compound was, however, characterized as the perchlorate, colourless prisms, m.p. 190°, from EtOH, ν_{max} cm^{-1} 3200–2300, 1740. (Found: C, 53·2; H, 5·45; N, 3·2; Cl, 8·45. $C_{19}H_{21}NO_4$, $HClO_4$ requires: C, 53·35; H, 5·2; N, 3·35; Cl, 8·3%). Basification of this salt yielded only resinous material.

2,3-Dimethoxy-7,8-dihydro-13-oxo-berberinium perchlorate. 35 (A = B = C = W = H; X = Y = OMe). 2-(3,4-Dimethoxybenzyl)1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (4·5 g) in polyphosphoric ester, prepared from P_2O_5 (30 g), $CHCl_3$ (30 ml) and ether (60 ml), was heated at 130° for 2·5 hr. The dark purple coloured soln was poured into water (300 ml) containing HCl (10 ml) and then made alkaline with NaOH aq. The yellow product which separated was collected and dissolved in EtOH (20 ml); addition of 60% perchloric acid (1 ml) to this soln caused the separation of colourless needles (3·0 g), m.p. 291–293°; λ_{max} (ε) nm, 228 (8400), 289 (36,000), 320 (7100) inflexion, 365 (2900); ν_{max} cm^{-1}, 1690; NMR ($CDCl_3$) ppm 9·15 singlet [1] (C_7-H), 8·5 singlet [1] (C_{12}-H) 7·9 complex [1] (C_1-H), ~7·5 complex [5] (aromatic protons), 4·7 triplet [2] J = 7·5 Hz ($\equiv\overset{+}{N}-CH_2-CH_2-$), 4·2, 4·1 two singlets [6] (2 × $-OCH_3$), 3·3 triplet [2] J = 7·5 Hz ($\equiv-CH_2-CH_2-$). (Found: C, 56·0; H, 4·7; N, 3·3; Cl, 8·4. $C_{19}H_{18}NO_3$, $HClO_4$ requires: C, 55·7; H, 4·6; N, 3·2; Cl, 8·4%). This compound was also obtained from the acid by a cyclization reaction using polyphosphoric acid, at 125° for 3 hr the yield of product being somewhat lower.

All attempts to effect the cyclization of 2-(2,3-dimethoxy)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, using polyphosphoric ester or polyphosphoric acid, failed.

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ISOPAVINE ALKALOIDS: SYNTHESIS AND BIOSYNTHETIC SPECULATIONS

(Tetrahedron Letters, 1969, 1515)

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ISOPAVINE ALKALOIDS: SYNTHESIS AND BIOSYNTHETIC SPECULATIONS

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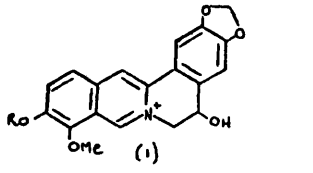
Considerable interest has been aroused by the recent isolation of the first two 5-hydroxyberberine alkaloids, berbastine (1, R = Me) from[1] Hydrastis canadensis L. and thalidastine (1, R = H) from[2] Thalictrum fendleri. Both plants also contain berberine, among other alkaloids, and it has been found[1b] that noradrenaline is an efficient precursor of



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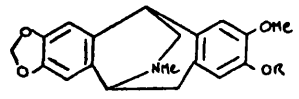

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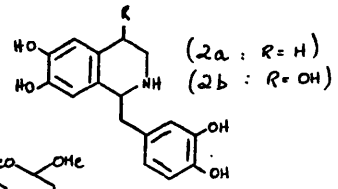
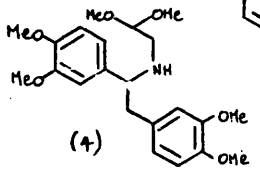


(2a : R = H)
(2b : R = OH)

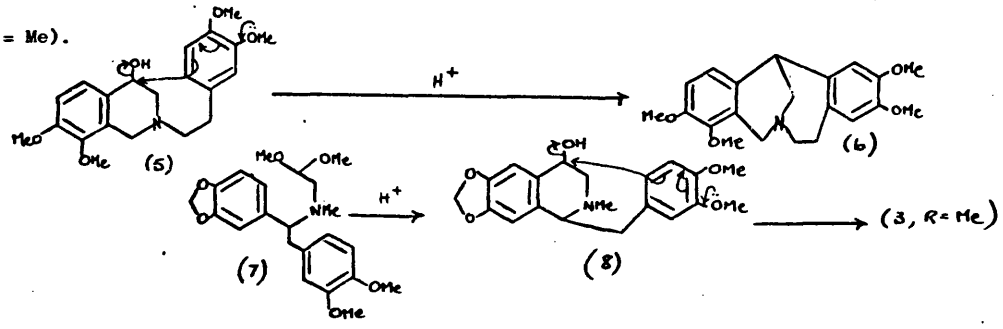


(4)

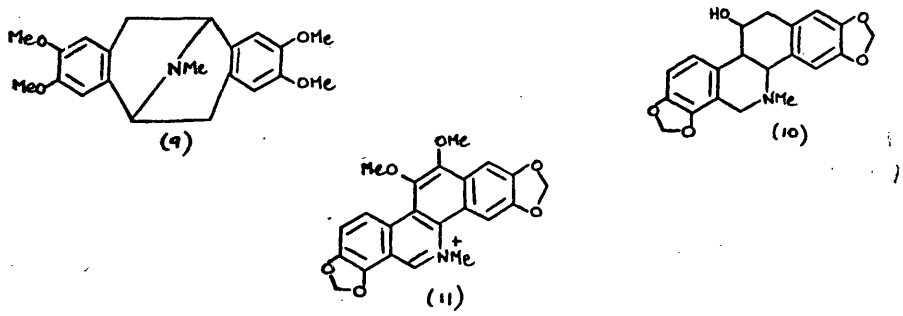
berberastine, but not of berberine, in H. canadensis. The conclusion that berberine is not a precursor of berberastine has led to the postulate[1b] that 4-hydroxynorlaudanosoline (2b) may be involved in the biosynthesis of berberastine. It is feasible that (2b), like norlaudanosoline (2a), is the precursor of a diverse group of alkaloids, one such substance, 5-hydroxytetrahydroberberine, has recently been detected[1b] in H. canadensis.

We recently observed[3] that when the 4-hydroxytetrahydroisoquinoline (5) was treated with acids the product obtained was (6), and we rationalised this result as shown. It is possible that isopavine[4] alkaloids e.g. amurensine (3:R = H), or amurensinine (3:R = Me) are formed in vivo from (2b) by a similar displacement of the hydroxyl group by the 1-benzyl substituent. In the laboratory the aminoacetal (7) when treated with conc. HCl at R.T. for five days gave amurensinine[5] (24%), and it is known[3,6] that 4-hydoxy-1,2,3,4-tetrahydroisoquinolines are formed when benzylacetaldehyde aminoacetals are treated with mineral acid.

So far, however, we have been unable to isolate (8) in the pure state; it rapidly cyclises to (3:R = Me).



It has been suggested[7] that pavine alkaloids, for example arge monine (9) are derived in Nature from norlaudanosoline (2a) but it is tempting to suggest that 4-hydroxynorlaudanosoline is involved. A dehydration reaction, which is known[3] to occur readily, would yield the 1,2-dihydroisoquinoline from which the formation of the pavine skeleton is straightforward[8].



It is now well established that the benzo[c]phenanthridine alkaloids, such as chelidonine (10) are derived in the plant from berberine, and it is possible that mecarpine (11) is formed via a 5-hydroxyberberine precursor.

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THE REARRANGEMENT OF 1-ALLYL-1,2-DIHYDROISOQUINOLINES

(Tetrahedron Letters, 1969, 1731)

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THE REARRANGEMENT OF 1-ALLYL-1,2-DIHYDROISOQUINOLINES

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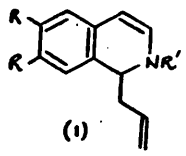
We have recently shown[1] that 1-allyl-2-methyl-1,2-dihydroisoquinoline (1, R = H, R' = Me) rearranges to the 3-allyl-2-methyl-3,4-dihydroisoquinolinium salt (2, R = H, R' = Me) when treated with dilute HCl. In a discussion of the chemistry of benzylaminoacetaldehyde dimethyl acetals we[2] have also reported that the compound (3, R = H), when treated with dilute HCl, is transformed into the 3-allyl-3,4-dihydroisoquinolinium salt (2, R = OMe, R' = H) in almost quantitative yield. Since we were able to isolate the 1-allyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (4), and since these compounds are easily dehydrated with acids, it was clear that the reaction proceeded via the 1,2-dihydroisoquinoline (1, R = OMe, R' = H). Knabe and Holtje, who[3] have just confirmed this finding, state their intention to study the mechanism of the reaction.

We have[2] viewed the reactions as an example of a suprafacial sigmatropic [3, 3] reaction, and have[4] supported this view by an examination of the reaction of (5) with dilute HCl under conditions similar to those used above. The 3-trans-crotyl-3,4-dihydroisoquinolinium salt (6) was formed[4] in 96% yield. An intramolecular course for the reaction is also supported by (a) the fact that when a mixture of (3, R = Me) and (5) was treated with dilute HCl, only the TWO products (2, R = OMe, R' = Me) and (6) were formed (GLC and mass spectral analysis and comparison with authentic specimens) and (b) the fact that the 1-propargyl-2-methyl-1,2-dihydroisoquinoline (7) rearranges to the allene derivative (8) when treated with HCl. [This latter experiment was conducted with Mr. F. L. Hall.]



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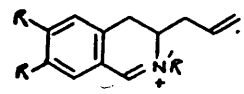

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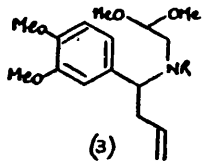

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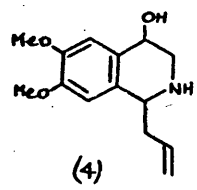

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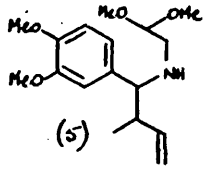

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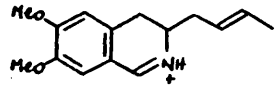

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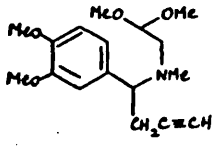

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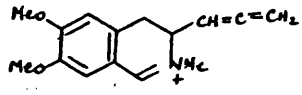

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5. Satisfactory analytical and spectral data have been secured for all new compounds described.

1,2-DIHYDROISOQUINOLINES

THE REACTION WITH *o*-NITROBENZALDEHYDES

(Tetrahedron, 1969, 25, 5365)

Tetrahedron. Vol. 25, pp. 5365 to 5373. Pergamon Press 1969. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XII[1]
THE REACTION WITH *O*-NITROBENZALDEHYDES

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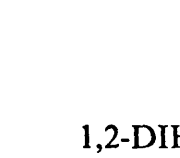
Abstract—The reaction between 1,2-dihydroisoquinolines and *o*-nitrobenzaldehydes has been shown to produce, in low yields, 4-[3-anthranilyl]isoquinolines. A new synthesis of 7*H*-dibenz[*de*,*g*]isoquinoline derivatives is also described.

IN PART X of this series[2] we described our results in the study of the interaction of 1,2-dihydroisoquinolines (**1**, R = H or Me) with a variety of aldehydes to form 4-substituted isoquinolinium salts of the type **2** (R = H or Me). The enamine was prepared either by reduction of isoquinoline salts with LAH, or by the cyclization of benzylaminoacetaldehyde acetals (**3**). We mentioned that some anomolous results had been obtained when *o*-nitrobenzaldehydes were used, and we now wish to report on these reactions.



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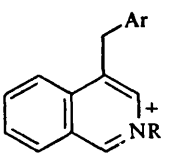

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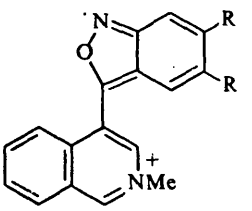

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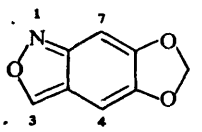

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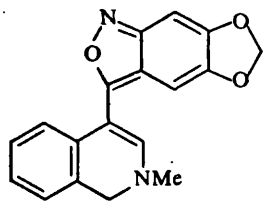
When 2-methyl-1,2-dihydroisoquinoline (**1**, R = Me) was reacted with 6-nitropiperonal in the presence of 6N HCl under the conditions described previously,[2] a 22% yield of a quaternary salt was isolated, which analysed for $C_{18}H_{13}N_2O_3Cl$; the expected product, **2** (R = Me, Ar = 2-nitro-4,5-methylenedioxyphenyl), has a molecular formula of $C_{18}H_{15}N_2O_4Cl$. The band at about 1510 cm^{-1} in the IR spectrum expected for the nitro group was absent. The NMR spectrum (Fig. 1), measured in CF_3CO_2H solution, exhibited one proton singlets at 9·3 ppm and 8·5 ppm, downfield from internal TMS, typical of the C_1 and C_3 H atoms of an isoquino-

linium salt. A two proton singlet at 6·0 ppm and a three proton singlet at 4·6 ppm were readily assigned to the methylenedioxy and $\rightarrow N^+$—Me groups respectively. The absorption expected at about 4·2 ppm for a methylene group at C_4 in structure **2** (R = Me) was absent and, although the total number of aromatic protons required for this structure were present, two one proton singlets at 6·6 ppm and 6·8 ppm were at rather higher field than expected. It is well known that *o*-nitrobenzaldehydes and *o*-nitroacetophenones are easily reduced to anthranils, and structure **4** (R,R = CH_2O_2) for the enamine reaction product was an obvious choice. The protons at C_4 and C_7 of 5,6-methylenedioxyanthranil (**5**) absorb at 6·8 ppm.

Anthranils typically form complexes with $HgCl_2$, and compound **4** (R,R = CH_2O_2) behaves similarly; a complex is also formed with $SnCl_2$. As expected,[4] sodium borohydride reduces **4** (R,R = CH_2O_2) to the 1,2-dihydroisoquinoline (**6**), whose structure follows from analytical and spectral data. The NMR spectrum is reproduced as Fig. II. 2-Methyl-4-(*o*-nitrobenzoyl)-1,2-dihydroisoquinoline **7** (R = NO_2, R′ = R″ = H),



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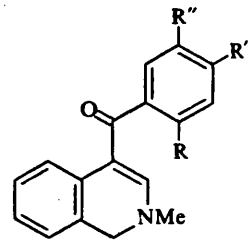

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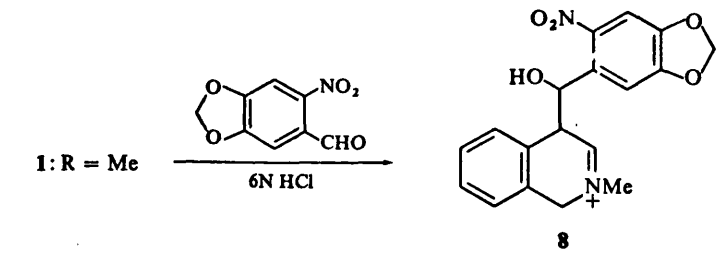
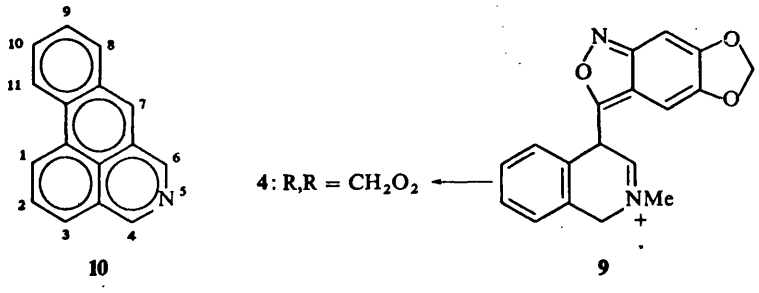
obtained[5,6] by the acylation of **1** (R = Me), has been reduced with $SnCl_2$/HCl to a compound whose analytical and spectral characteristics are in accord with the $SnCl_2$ complex of the anthranil **4** (R = H). A direct correlation between this product and the substance formed from **1** (R = Me) and *o*-nitrobenzaldehyde is, unfortunately, not possible since the latter gave the expected enamine product **2** (R = Me, Ar = *o*-nitrophenyl).

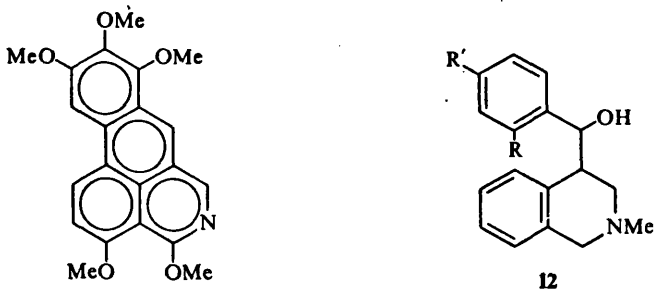
Analogous anthranil structures were produced when *o*-nitrobenzaldehyde, 6-nitropiperonal and 6-nitroveratraldehyde were reacted with some benzylaminoacetals of the type **3** under the conditions[2] which had been used previously for the formation of 4-benzylisoquinoline derivatives. These results are collected into Tables 1 and 1A.

Several mechanisms are possible for the formation of these 4-[3-anthranilyl]-isoquinolines. 1,2-Dihydroisoquinolines are known to be reducing agents, and it is possible that an anthranil is first formed which then reacts further with more 1,2-dihydroisoquinoline. However, when the anthranil **5** was reacted with **1** (R = Me) under the conditions of the original condensation, only black tars were formed. An alternative mechanism involves the condensation of the aldehyde with the 1,2-dihydroisoquinoline in the usual way[7] to form **8**, which is then further reduced by excess enamine; *o*-nitrobenzylalcohols are known[3] to yield anthranils on reduction. A possible sequence of events is shown in **1** (R = Me) → **9** → **4** (R,R = CH_2O_2).

One of our original reasons for attempting the preparation of 4-(*o*-nitrobenzyl)-







isoquinolines was the intention to develop new routes to the little studied dibenz[*de*,*g*] isoquinoline system **10**. The first synthesis in this series was achieved by Pschorr,[8] and the derivative **11** has also been described.[9] We have attained our objective by carrying out a Pschorr ring-closure on **12** (R = NH_2, R′ = H), thus forming the tetracyclic compound **13**; subsequent dehydration yielded **14**. The structure **14** has been confirmed by an alternative synthesis from the anhydride[8] **15** (Z = 0); treatment of this material with methylamine yielded **15** (Z = NMe), which, on reduc-

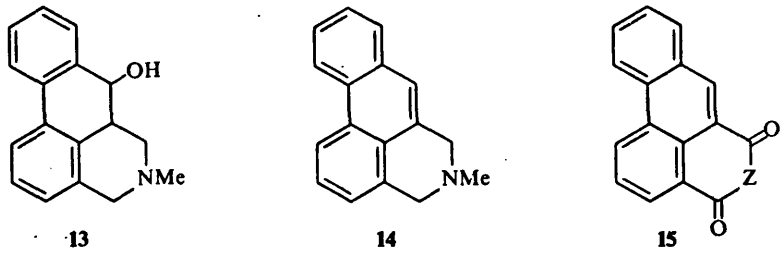


TABLE 1. SPECTRA OF 4(3′-ANTHRANILYL)-ISOQUINOLINIUM CHLORIDES

Substitution pattern	UV (Ethanol)	IR (Nujol)	NMR (CF_3CO_2H)							
	λ_{max} (ε) nm	ν_{max} cm^{-1}	C_1—H	C_3—H	C_8—H	C_6—H	C_5—H	C_4—H, C_7—H	—OCH_2O—	—OCH_3
6,7,5′,6′-Tetramethoxy-	253 (32,880), 320 (16,850)	1615	9·1	8·4	7·5		7·5	6·7, 6·8		4·0
6,7-Dimethoxy-5′,6′-methylenedioxy	252 (31,650), 320 (15,680)	1620	9·0	8·4	7·8		7·8	6·7	5·9	4·0
7,8-Dimethoxy-5′,6′-methylenedioxy-	260 (27,500), 310 (12,330)	1660, 1620	9·9	8·7		8·2	8·2	6·8, 7·0	6·1	4·3
7-Methoxy-8-hydroxy-5′,6′-methylenedioxy-	233 (33,220), 350 (16,120)	3400, 1620	9·5	8·3		7·8	7·8	6·6, 6·7	5·9	4·1
6,7-Dimethoxy-	247 (24,600), 312 (12,700)	1620	8·8	8·6	Broad absorption ~7·6 [6]					

TABLE 1A. ANALYTICAL DATA OF 4-(3′-ANTHRANILYL)-ISOQUINOLINIUM CHLORIDES

Substitution pattern	m.p. (EtOH)	% yield	Analytical results								
			Found				Requires				
			C	H	N	Cl	Mol Formula	C	H	N	Cl
6,7,5′,6′-Tetramethoxy-	218–219° (yellow needles)	10	59·2	4·9	6·6	8·3	$C_{20}H_{19}N_2O_5Cl$	59·5	4·7	6·9	8·8
6,7-Dimethoxy-5′,6′-methylenedioxy-	222–223° (pale yellow prisms)	18	59·0	4·2	7·0	9·4	$C_{19}H_{15}N_2O_5Cl$	59·0	3·9	7·25	9·2
7,8-Dimethoxy-5′,6′-methylenedioxy-	255–257° (yellow prisms)	13	59·1	4·2	7·1	9·0	$C_{19}H_{15}N_2O_5Cl$	59·0	3·9	7·25	9·2
7-Methoxy-8-hydroxy-5′,6′-methylenedioxy-	255–257° (bright yellow needles)	26	57·5	3·7	7·1	9·0	$C_{18}H_{13}N_2O_5Cl$	57·65	3·5	7·5	9·5
6,7-Dimethoxy-	216–218° (yellow prisms)	9	61·4	4·2	7·7	10·1	$C_{17}H_{15}N_2O_3Cl$	61·0	4·5	8·3	9·5

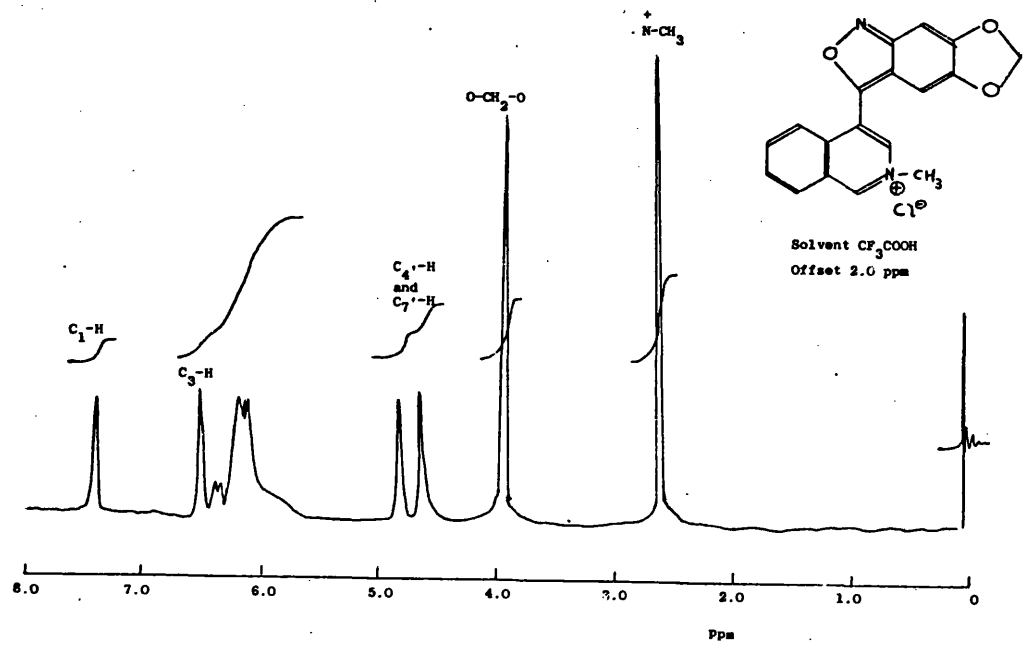
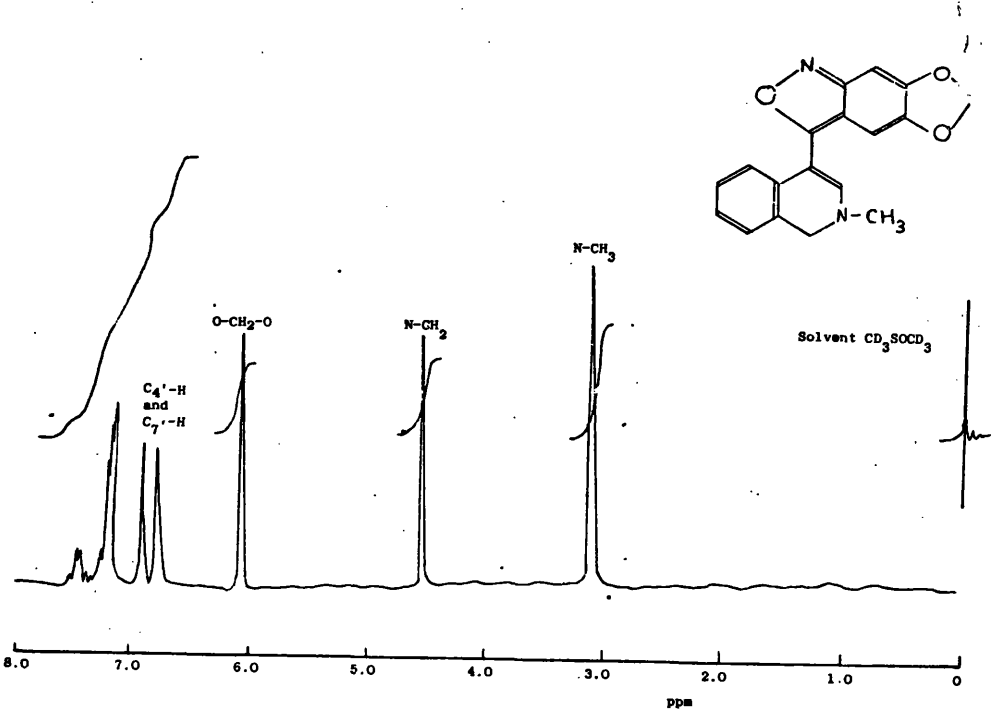

+
N-CH3
O-CH2-O
C1-H
C3-H
C4'-H
and
C7'-H
N-CH3
Cl⊖
Solvent CF3COOH
Offset 2.0 ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Ppm

FIG. 1


N-CH3
O-CH2-O
N-CH2
N-CH3
C4'-H
and
C7'-H
Solvent CD3SOCD3
8.0
7.0
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5.0
4.0
3.0
2.0
1.0
0
ppm

FIG. 2

tion with LAH gave a product, identical (mixed m.p., superimposable IR spectra) with the compound obtained above. The required starting material **12** (R = NH_2, R′ = H) was easily obtained by first reducing **7** (R = NO_2, R′ = R″ = H) to **12** (R = NO_2, R′ = H) with $NaBH_4$, followed by further reduction with LAH.

We are now developing the synthesis of *7H*-dibenz[*de,g*]isoquinolines, when we hope to examine their chemical, spectral and biological properties.

EXPERIMENTAL

5,6-Methylenedioxyanthranil (**5**) 6-Nitropiperonal (10 g) was added portionwise to a soln of $SnCl_2$ (30 g) in concd HCl (75 ml) at 0°. After 2 hr the product was collected by filtration, yield 7·g (84%), m.p. 110–112°: λ_{max} (ε) nm, 310 (1,410): ν_{max} cm^{-1}, 1640 (>C=N—), 1600 (>C=C<), 1200 (—O CH_2 O—); NMR (CD_3SOCD_3) ppm, 9·3 s [1](C_3—H), 6·9 s [1] and 6·7 s [1] (C_4—H and C_7—H), 6·0 s [2] (—O CH_2 O—). Formation of mercuric chloride complex was achieved by the addition of mercuric chloride (0·3 g) in EtOH (60 ml) to a soln of the anthranil (0·5 g) in EtOH (30 ml). The solid product recrystallized from EtOH as red needles (0·45 g), m.p. 231–233°, λ_{max} (ε) nm, 310 (4,850) ν_{max} cm^{-1}, 1660 (>C=N^+<), 1610 (>C=C<). NMR (DCl) ppm 9·8 s [1] (C_3—H), 7·5 s [1] and 7·4 s [1] (C_4—H and C_7—H), 6·7 s [2] (—O CH_2 O—). [[Found: C, 21·6; H, 1·4; N, 3·1; Cl, 15·8 $C_8H_5NO_3Cl_2Hg$ requires: C, 22·0; H, 1·1; N, 3·2; Cl, 16·3%].

General preparation of 4-(3′-anthranilyl)isoquinolinium chlorides. The appropriately substituted benzylaminoacetaldehyde dimethyl acetal (5 g) was heated under reflux with the *o*-nitrobenzaldehyde (molar equiv), EtOH (50 ml) and conc HCl (25 ml); the soln being protected by an atmosphere of N_2. After 30 min, the soln was allowed to cool, when the product anthranil separated. Recrystallization was achieved from EtOH in each case.

4-(5′,6′-Methylenedioxy-3′-anthranilyl)2-methylisoquinolinium chloride, (**4**), 2-Methyl-1,2-dihydroisoquinoline (5·5 g) in ether was added to 6-nitropiperonal (6·7 g) in EtOH (80 ml) and conc HCl (25 ml). After heating, at reflux under N_2 for 4 hrs, the soln was evaporated to small bulk, and cooled. The yellow crystals of product which separated were collected and recrystallized from EtOH, yield 3·1 g (22%), m.p. 246–248°: λ_{max} (ε) nm 240 (10,600): ν_{max} cm^{-1}, 1660 (>C=N^+<), 1640 (>C=N—), 1600 (>C=C<), 1240 (—O CH_2 O—); NMR (CF_3CO_2H) ppm, 9·3 s [1] (C_1—H), 8·5 s [1] (C_3—H), ~ 8·0 m [4] (aromatic protons), 6·7 broad s [2] (C_4'—H, C_7'—H), 6·0 s [2] (—O CH_2 O—), 4·6 s [3] (>N^+—CH_3). [Found: C, 63·0; H, 3·8; N, 7·8; Cl, 10·9 $C_{18}H_{13}N_3O_3Cl$ requires: C, 63·2; H, 3·8; N, 8·2; Cl 10·5%].

This compound was characterized as the mercuric chloride complex, the yellow product being recrystallized from EtOH m.p. 242–244°. [Found: C, 35·5; H, 2·0, N, 4·8; Cl, 17·0 $C_{18}H_{13}N_2O_3Cl_3Hg$ requires: C, 35·3; H, 2·1; N, 4·6; Cl, 17·3%].

4-(5′,6′-Methylenedioxy-3′-anthranilyl) 2-methyl-1,2-dihydroisoquinoline, (**6**). The anthranil (0·8 g) in EtOH (50 ml) was treated with a two molar amount of $NaBH_4$ (2 g) and the soln heated under reflux for 2 hrs. Water was then added and the mixture extracted several times with $CHCl_3$. Removal of the solvent from the combined extracts afforded crude **6**, which was recrystallized from EtOH as pale yellow prisms 0·7 g (96%), m.p. 190–192°; λ_{max} (ε) nm, 240 (18,000): ν_{max} cm^{-1}, 1655 (>C=C<), 1620 (>C=N—), 1610 (>C=C<), 1200 (—O CH_2 O—); NMR (CD_3SOCD_3) ppm, 7·4–7·1 complex [5] (aromatic protons); 6·9 s [1] and 6·8 s [1] (C_4'—H and C_7'—H); 6·1 s [2] (—O CH_2 O—); 3·0 s [3] (>N—CH_3). [Found: C, 70·5; H, 4·7; N, 9·2 $C_{18}H_{14}N_2O_3$ requires: C, 70·6; H, 4·6; N, 9·1%], MW (mass spec) obs. 306, calc. 306.

Treatment of 4-(3′-anthranilyl) isoquinolinium chlorides with sodium borohydride. Reaction of the salts with this reagent gave only the corresponding free bases, whose physical and analytical properties are listed below:

4-(5′,6′-Dimethoxy-3′-anthranilyl) 6,7-dimethoxyisoquinoline, m.p. 241–242° (EtOH), λ_{max} (ε) nm, 225 (29,860), 350 (11,200): ν_{max} cm^{-1}, 1630 (>C=N—), 1600 (>C=C<); NMR ($CDCl_3$) ppm, 9·0 s [1] (C_1—H); 8·7 s [1] (C_3—H); 7·3 s [1] and 7·5 s [1] (C_5—H and C_8—H); 6·7 s [1] and 6·8 s [1] (C_4'—H

and C_7—H); 4·0 broad s [12] (—O CH_3). [Found: C, 65·2; H, 4·9; N, 7·3 $C_{20}H_{18}N_2O_5$ requires: C, 65·6; H, 4·95; N, 7·65%.]

4-(*5′,6′-Methylenedioxy-3′-anthranilyl*) 7,8-*dimethoxyisoquinoline* m.p. 267–269°, λ_{max} (ε) nm, 246 (40,000): ν_{max} cm^{-1}, 1620 (>C=N—), 1615 (>C=C<); NMR (CF_3CO_2H) ppm, as for parent salt. [Found: C, 65·2; H, 3·9; N, 8·1 $C_{19}H_{14}N_2O_5$ requires: C, 65·2; H, 4·0; N, 8·0%.]

Reduction of 4-(2-nitrobenzoyl) 2-methyl-1,2-dihydroisoquinoline

(a) *The benzoyldihydroisoquinoline* (1 g) was reacted with warm $SnCl_2$ aq (5 g) in conc HCl (20 ml). After 2 hr at 100° the soln was allowed to cool and the deep orange ppt of 4-(-3′-anthranilyl) 2-methylisoquinolinium chloride–stannous chloride complex which separated was then collected, and recrystallized from DMSO, yield 25% as yellow plates, m.p. 275–277°; λ_{max} (ε) nm, 223 (35,000): ν_{max} cm^{-1}, 1660 (>C=N^+<), 1610, 1600 (>C=C<); NMR (CD_3SOCD_3) ppm, 9·6 s [1] (C_1—H); 8·5–7·0 complex [9] (aromatic protons); 4·4 s [3] (>N^+—CH_3). [Found: C, 42·2; H, 2·9; N, 6·0; Cl, 22·2 $C_{17}H_{13}N_2OCl$ requires: C, 41·9; H, 2·7; N, 5·8; Cl, 21·8%].

(b) The benzoyldihydroisoquinoline was reduced by heating in aqueous EtOH soln with excess $NaBH_4$. After 2 hr the soln was cooled, diluted with water and extracted several times with $CHCl_3$. Removal of the solvent from the combined extracts afforded 12 (R = NO_2, R = H) as colourless prisms which was recrystallized from EtOH, yield 23% m.p. 187–189°, λ_{max} (ε) nm, 265 (6,000): ν_{max} cm^{-1}; ~3500 (—OH), 1610 (>C=C<), 1520 (—NO_2); NMR ($CDCl_3$) ppm, 7·9 m [1] (aromatic proton adjacent to —NO_2 group); 7·5–6·9 m [7] (aromatic protons); 5·8 broad s [2] (—OH and —CHAr); 4·2–2·6 complex [5] (aliphatic protons); 2·5 s [3] (N—CH_3). [Found C, 68·2; H, 6·1; N, 9·2 $C_{17}H_{18}N_2O_3$ requires: C, 68·4; H, 6·1; N, 9·4%]. Acetate derivative: colourless needles m.p. 89–91° (EtOH). [Found: C, 67·3; H, 6·1; N, 8·1 $C_{19}H_{20}N_2O_4$ requires: C, 67·1; H, 5·9; N, 8·2%.]

The above tetrahydro alcohol (3 g) in dry ether (100 ml) was treated with small portions of LAH (total 3 g). After stirring at room temp for 4 hr, the excess reagent was destroyed by the cautious addition of 30% sodium potassium tartrate soln. After filtration the ethereal soln was evaporated to yield **12** (R = NH_2, R′ = H) as a red oil (2·3 g). This compound was not purified but used directly in subsequent experiments.

In a similar experiment to (b) above, 7[6] (R = R″ = H, R′ = NO_2) gave 30% of **12** (R = H, R′ = NO_2) m.p. 197–199° (EtOH); λ_{max} (ε) nm 280 (9,200): ν_{max} cm^{-1}, 3200 (—OH) 1600 (>C=C<), 1510 (—NO_2); NMR ($CDCl_3$) ppm, 8·2–7·1 complex [8] (aromatic protons); 5·8 broad s [1] (—CH—Ar); 5·4 broad s [1] (—OH, removed by deuteration); 4·2–3·3 q [2], J = 15 H_z (Ar—C(H)(H)—N); 3·5–2·7 complex [3] (N—CH_2—CH—); 2·55 s [3] (N—CH_3). [Found: C, 68·4; H, 5·9; N, 9·2 $C_{17}H_{18}N_2O_3$ requires: C, 68·4: H, 6·1; N, 9·4%].

This compound was characterized as the O-acetate by heating with Ac_2O for 30 min at 100°, yield 76%, colourless prisms m.p. 137–139° (EtOH); λ_{max} (ε) nm 272 (7,200): ν_{max} cm^{-1}, 1725 (CH_3CO_2—), 1600 (>C=C<), 1250 (CH_3CO_2—); NMR ($CDCl_3$) ppm, 8·3–7·1 m [8] (aromatic protons); 6·2 broad s [1] (—CH—Ar) 4·1–3·0 q [2], J = 15 H_z (Ar—C(H)(H)—N); 3·0–2·4 m [3] (>N—CH_2—CH—), 2·3 s [3] (>N—CH_3); 2·0 s [3] (CH_3—CO_2—). [Found: C, 66·9; H, 5·9; N, 8·1 $C_{19}H_{20}N_2O_4$ requires: C, 67·1; H, 5·9; N, 8·2%.]

Pschorr ring closure of **12** (R = NH_2, R′ = H). The amine (2·3 g) was dissolved in 2N HCl (140 ml) and diazotized at 0° by the addition of $NaNO_2$ (0·6 g) in ice cold water (50 ml). After 1 hr at 0°, urea (0·2 g) was added followed by Cu powder (2 g). At the end of a further 3 hr the suspension was filtered, basified with NaOH aq and extracted with $CHCl_3$ (3 × 30 ml). The combined extracts were dried and evaporated to give **13** as a brown gum, which crystallized on trituration with $CHCl_3$ as colourless needles (0·55 g), m.p.

176–177° ($CHCl_3$); λ_{max} (ε) nm, 273 (5,000); ν_{max} cm^{-1}, 1610, 1590 (>C=C<), 3300 (—OH); NMR (CD_3SOCD_3) ppm, 7·9–7·0 m [7] (aromatic protons); 4·5 broad s [1] (HO—C(Ar)—H); 3·9–2·7 m [5] (—CH_2—N—CH_2, C_4—H); 2·4 s [3] (—NCH_3). [Found: C, 81·35; H, 7·1; N, 6·0 $C_{17}H_{17}NO$ requires: C, 81·2; H, 6·8; N, 5·6%.]

Dehydration of **13**. A soln of the above alcohol (0·5 g) in $CHCl_3$ (50 ml) was saturated with HCl. Removal of the solvent and basification of the residue gave **14** as a colourless solid (0·3 g), which crystallized from $CHCl_3$ as small prisms, m.p. 99–101°, λ_{max} (ε) nm, 226 (24,000), 258 (60,000), 302 (16,000), λ_{max} cm^{-1}, 1615 (>C=C<); NMR ($CDCl_3$) ppm, 8·5 multiplet [2] (C_1—H and C_{11}—H); 7·6–7 multiplet [6] (aromatic protons); 3·75 s [4] (2 × (>N—CH_2—); 2·4 s [3] (>N—CH_3). [Found: C, 87·5; H, 6·5; N, 6·0 $C_{17}H_{15}N$ requires: C, 87·5; H, 6·5; N, 6·0], M.W. (mass spec): obs. 233 requires 233.

5-Methyl-4,6-diketodibenz[de,g]*isoquinoline* (**15**, Z = NMe). To a warm 30% aqueous soln of $MeNH_2$ (10 ml) 4,6-diketophenanthro [1,10*c*–*d*] pyran[8] (2 g) was added with stirring. After 30 min the soln was filtered and the solid product recrystallized from MeOH to give **15** (Z = NMe) as colourless cubes (2·1 g) m.p. 221–222° λ_{max} (ε) nm 240 (15,000), 265 (12,000), 340 (9,000), ν_{max} cm^{-1}, 1710, 1670; NMR ($CDCl_3$) ppm, ~8·7 m [4] (C_1—H, C_3—H, C_7—H, C_{11}—H); ~7·7 m [4] (C_2—H, C_8—H, C_9—H, C_{10}—H); 3·5 s [3] (NCH_3). [Found: C, 77·8; H, 4·4; N, 5·1 $C_{17}H_{11}NO_2$ requires: C, 78·1; H, 4·25; N, 5·3%].

5-Methyl-4,6H-dibenz[d,e]*anthracene* (**14**) LAH (1·5 g) was added in small portions to a suspension of the above product (0·3 g) in ether (150 ml). After heating under reflux for 48 hr the soln was cooled and excess reagent destroyed by the addition of 30% sodium potassium tartrate soln. After filtration the etherial soln was evaporated to yield **14** as a colourless solid which recrystallized from $CHCl_3$ as needles (0·17 g) m.p. 99–100°. This compound was identical spectroscopically and chemically with the compound previously obtained from **12** (R = NH_2, R′ = H).

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Tetrahedron. Vol. 26, pp. 2239 to 2247. Pergamon Press 1970. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XIV[1]

ALKYLATION

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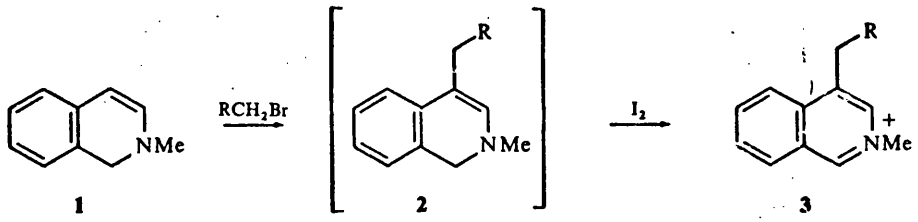
Abstract—The reactions between 2-methyl-1,2-dihydroisoquinoline and various alkyl halides have been studied, and the preparation of 4-substituted isoquinolines from 4-lithioisoquinoline has been explored.

IN PART VI[2] we reviewed and developed some methods for C_4-benzylation of isoquinoline derivatives and mentioned that we had succeeded in preparing 2-methyl-4-benzylisoquinolinium iodide (3, R = C_6H_5) from 2-methyl-1,2-dihydroisoquinoline (1) and benzyl bromide, followed by oxidation of the intermediate (2) with iodine. We have now examined this fundamental[3] alkylation reaction of enamines in more detail.



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The results, collected into Table 1, were obtained under essentially standard conditions in which equimolar amounts of the enamine (1) and the alkyl halide in ethanol solution containing one mole of triethylamine were heated under reflux for 4 hr. To this mixture was added iodine and potassium acetate to effect dehydrogenation. The product quaternary salts were isolated as crystalline solids; attempts to identify other products present in the residual dark oils usually failed, although small additional amounts of the main products were sometimes obtained. The structures of the products listed in Table 1 were allocated on the basis of analytical and spectral data; the NMR spectra were especially informative (Table 2). Although yields are seemingly low, they compare favourably with those expected if the more traditional synthetic routes were adopted.

Of all the types of alkyl halide studied, benzyl bromides were the most successful, although rather surprisingly *o*-methoxybenzyl bromide failed to yield a C-benzylated

1,2-DIHYDROISOQUINOLINES - ALKYLATION

(Tetrahedron, 1970, 26, 2239)

TABLE 1. 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS

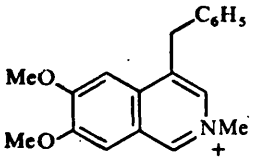
No.	-C_4-substituent	M.p.	Mol. Formula	% Yield§	Analysis							
					Calculated				Found			
					C	H	N	I	C	H	N	I
1	$C_6H_5CH_2$—	185–186°	$C_{17}H_{16}NI$	27	56·5	4·5	3·9	35·1	56·7	4·7	3·7	35·25
2	*o*-$O_2NC_6H_4CH_2$—	188–189°	$C_{17}H_{15}N_2O_2I$	14*	50·2	3·7	6·9	31·3	50·6	4·1	6·9	30·45
3	*m*-$O_2NC_6H_4CH_2$—	245–246°	$C_{17}H_{15}N_2O_2I$	21	50·2	3·7	6·9	31·3	50·4	4·0	6·7	30·8
4	*p*-$O_2NC_6H_4CH_2$—	236–237°	$C_{17}H_{15}N_2O_2I$	23	50·2	3·7	6·9	31·3	50·1	4·3	7·1	30·6
5	*m*-$MeOC_6H_4CH_2$—	199–200°	$C_{18}H_{18}NOBr$‡	5*	62·8	5·7	4·1	—	62·4	5·7	3·8	—
6	*p*-$MeOC_6H_4CH_2$—	235–236°	$C_{18}H_{18}NOI$	25	55·0	4·6	3·6	32·5	55·2	4·3	3·8	32·3
7	$C_6H_5CH\ CH_3$	99–100°	$C_{18}H_{18}NI_3$†	11	34·4	2·9	2·2	60·5	33·9	2·6	2·5	61·3
8	*o*-$ClC_6H_4CH_2$—	189–190°	$C_{17}H_{15}NICl$	9*	51·7	3·8	3·55	32·2	51·6	4·1	3·7	32·5
9	*p*-$ClC_6H_4CH_2$—	202–203°	$C_{17}H_{15}NICl$	19	51·7	3·8	3·55	32·3	51·5	4·1	3·6	32·15
10	*p*-$MeC_6H_4CH_2$—	195–196°	$C_{18}H_{18}NI$	10*	57·65	4·8	3·7	33·8	57·5	5·1	3·8	33·95
11	$C_6H_5COCH_2$—	241–242°	$C_{18}H_{16}NOBr$‡	13	63·1	4·7	4·1	23·4	62·9	4·8	4·2	23·8
12	3,4-$(MeO)_2C_6H_3COCH_2$—	229–230°	$C_{20}H_{20}NO_3I$	17	59·8	5·0	3·5	19·95	59·3	4·9	3·6	20·3
13	3,4-CH_2O_2-6-$NO_2C_6H_2CH_2$—	219–221°	$C_{18}H_{15}N_2OI$	15	48·0	3·3	6·2	28·2	48·0	3·5	6·8	28·6

* Without triethylamine. ‡ Isolated as bromide. † Isolated as periodide. § Based on isoquinoline methiodide.

TABLE 2. SPECTRAL DATA FOR 2-METHYL-4-ALKYLISOQUINOLINIUM SALTS

No.	NMR (in CF_3CO_2H)				IR cm^{-1}	UV λ_{max} nm (ε_{max})
	C_1	C_3	C_4—CH_2—	NCH_3		
1	8·68	8·5	5·2	3·89	1645, 1610	233(49,000), 283(4,250), 340(5,100)
2	9·41		4·96	4·41	1650, 1610, 1525, 1350	234(48,700), 270(2,020), 340(6,740)
3	9·75		4·66	4·46	1650, 1610, 1530, 1350	234(42,100), 270(3,350), 340(3,500)
4	9·63	7·66	4·83	4·66	1650, 1610, 1510, 1350	233(38,200), 270(6,680), 340(5,250)
5	9·48		4·63	4·5	1650, 1610, 1560	234(56,200), 283(7,000), 340(6,950)
6	9·50		4·60	4·5	1650, 1610, 2840	233(58,400), 284(6,950), 340(5,050)
7	9·91	8·7		4·5	1650, 1610	232(51,400), 293(9,720), 342(4,450)
8	9·47		4·74	4·5	1650, 1610	234(49,000), 284(2,580), 341(5,260)
9	9·47		4·58	4·53	1650, 1610	229(56,300), 293(6,540), 342(5,720)
10	9·41		4·58	4·53	1650, 1610	222(52,300), 230(49,700), 281(6,340), 340(6,260)
11	9·56		5·02	4·66	1685, 1650, 1610	—
12	9·50		5·16	4·58	1645, 1630, 1510, 1030	233(40,100), 278(12,500), 348(3,000)
13	9·40		4·95	4·5		—

product. With 6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline and benzyl bromide, the yield of **4** was 48%. Of particular interest to us was the success with ω-bromoacetophenones, which yielded compounds of the type **5**, previously prepared[4] by the interaction of 1,2-dihydroisoquinolines and phenylglyoxals.



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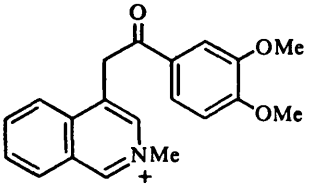

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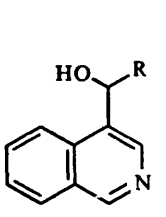
We were unable to isolate any C_4-alkylated products when **1** was reacted with ethyl chloroformate, allyl bromide, propargyl bromide or simple aliphatic halides. With allyl and crotyl halides, the N-allylated-1,2,3,4-tetrahydroisoquinolines were the only identifiable products.

From the above studies we conclude that the reaction between 1,2-dihydroisoquinolines and aryl aldehydes[5] is a superior method for the preparation of 4-benzylisoquinoline derivatives. A modified procedure, leading to 4-benzyl-1,2,3,4-tetrahydroisoquinolines has recently[6] been described, based upon a reaction first described by Grewe *et al.*[7] Some of this latter work has been corrected.[8]

Some time ago the preparation of isoquinoline-4-carboxylic acid was described[9] involving the carbonation of 4-lithioisoquinoline, obtained from 4-bromoisoquinoline.[10] Our interest in 4-substituted isoquinolines prompted a study of the scope of 4-lithioisoquinoline as a synthetic intermediate. It has now been successfully reacted with the carbonyl compounds listed in Table 3. The expected alcohols were obtained in each case and their structures follow from elemental and spectral analysis; NMR spectra are diagnostic in some cases, for example for **6**(R = *p*-methoxyphenyl) (Table 4). The compounds obtained from acetone[12] and from acetophenone[12,13]



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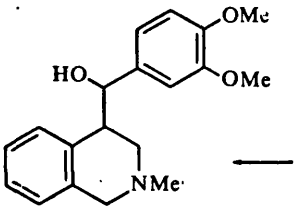

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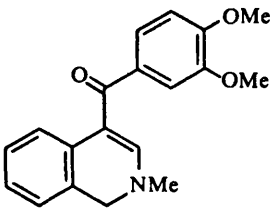

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are known compounds. The products resulting from 4-lithioisoquinoline and acetaldehyde and benzaldehyde (**6**, R = CH_3 and C_6H_5) respectively, were oxidized to the known 4-acetyl[12] and 4-benzoylisoquinolines.[12,13] The compound **6** (R = 3,4-$(MeO)_2C_6H_3$) obtained from veratraldehyde was N-methylated and reduced with

TABLE 3. THE REACTION OF 4-LITHIOISOQUINOLINE WITH CARBONYL COMPOUNDS

No.	Carbonyl compound	% Yield†	Product Mol. Formula	M.p.	Analysis Calculated C	H	N	I	Found C	H	N	I
1	CH_3CHO	72	$C_{11}H_{11}NO$	177°*	45·7	4·4	4·4	40·5	46·0	4·3	4·5	40·5
2	$(CH_3)_2CHCHO$	58	$C_{13}H_{15}NO$	125–126°	77·6	7·5	7·0	—	77·5	7·55	6·7	—
3	CH_3COCH_3	65	$C_{12}H_{13}NO$	108–109°	77·0	7·0	7·5	—	76·3	7·3	7·9	—
4	$CH_3COCH_2CH_3$	51	$C_{13}H_{15}NO$	215–216°*	49·1	5·25	4·1	37·0	49·4	5·5	3·9	36·9
5	Cyclohexanone	58	$C_{15}H_{17}NO$	179–180° 274–275°*	79·3	7·5	6·2	—	79·1	7·7	6·4	—
6	C_6H_5CHO	61·5	$C_{16}H_{13}NO$	213–215°*	54·1	4·3	3·7	33·65	54·4	4·5	3·8	34·0
7	m-$MeOC_6H_4CHO$	52	$C_{17}H_{15}NO_2$	184–185°*	53·0	4·4	3·4	31·2	52·75	4·7	3·6	31·2
8	p-$MeOC_6H_4CHO$	58	$C_{17}H_{15}NO_2$	128–129°	77·0	5·6	5·3	—	76·85	5·6	5·5	—
9	3,4-$(MeO)_2C_6H_3CHO$	58	$C_{18}H_{17}NO_3$	219–220°	52·6	4·6	2·9	—	52·3	4·8	3·5	—
10	p-Cl—C_6H_4CHO	54	$C_{16}H_{12}NOCl$	120–121°	71·4	4·5	5·2	Cl, 13·2	71·6	4·6	5·3	13·5
11	$C_6H_5COCH_3$	38	$C_{17}H_{15}NO$	167–168°	81·9	6·1	5·6	—	82·1	6·2	5·75	—
12	Acetoveratrone	53·3	$C_{19}H_{19}NO_3$	201–202°	73·7	6·15	4·6	—	73·4	6·0	4·8	—
13	Furfuraldehyde	48	$C_{14}H_{11}NO_2$	187–188°*	48·1	3·7	3·7	33·9	47·95	3·7	3·9	33·9
14	Pyridine-2-aldehyde	45	$C_{15}H_{12}N_2O$	148–150°	76·25	5·1	11·9	—	76·3	5·1	11·8	—
15	$(CH_3)_2NCHO$	68	$C_{10}H_7NO$	103°	76·4	4·5	8·9	—	76·2	4·7	8·7	—

* O-acetate methiodide

† Based on 4-bromoisoquinoline.

TABLE 4 SPECTRAL DATA OF 4-HYDROXY-ALKYLISOQUINOLINES

No.	NMR $C_1\underline{H}$	NMR C_3H	NMR —O<u>H</u>	Others	IR cm^{-1}	UV λ_{max} nm(ε_{max})
1	8·9	8·5	4·7	5·45q[1] (—CH—CH_3, J = 7 Hz) 1·6d[3] (—CH—CH_3, J = 7 Hz)	3,120, 1,630 1,590	—
2	8·85	8·45	4·55	4·88d[1] (—CH—, J = 7 Hz) 2·17m[1] (—CH(CH_3)(CH_3), J = 7 Hz) 1·0d[3], 0·75d[3] (2 × CH_3, J = 7 Hz)	3,260, 1.620, 1,580	219(33,000) 274(1,500) 311(1,440) 324(2,400)
3	9·0	8·3	4·45	0·755[3] (2 × CH_3)	3,270 1,620 1,590	219(33,800) 272(1,170) 309(1,040) 322(2,080)
4*	10·1	—	3·3	0·9t[3] (—CH_2CH_3) 1·8s[3] (—CH_3) 2·1q[2] (—CH_2CH_3) 4·7s[3] (=N—CH_3)	3,400 1,040 1,610	231(50,000) 280(3,350) 340(6,650)
5	8·9	8·3	2·92	1·9m[10] (5 × —CH_2—)	3,240 1,620 1,585	220(33,600) 273(1590) 310(1,275) 322(2,400)
6	9·1	8·62	5·0 Broad	6·25[1] (—CH—)	3,150, 1,625 1,590	220(37,500) 273(1,360) 310(1,190) 323(2,380)
7	8·95	8·45	4·45	6·3s[1] (—CH—), 3·68[3] (—OCH_3)	3,200 1,625 1,600	220 274 310 323

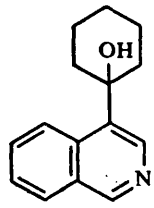
TABLE 4—*continued*

No.	NMR				UV	
	$C_1\underline{H}$	$C_3\underline{H}$	—O<u>H</u>	Others	IR cm^{-1}	λ_{max} nm(ε_{max})
8	9·7	8·8	—	3·95[3] (O—C<u>H</u>$_3$)	3,300	220(51,400)
					1,630	275(5,620)
					1,590	310(3,610)
						323 (4,820)
9	9·4*	8·6	—	2·3s[3] (OCOC<u>H</u>$_3$) 4·5[1] (C<u>H</u>)	1,750	206(27,500)
				3·9s[6] (2 × OC<u>H</u>$_3$)	1,640	232(29,700)
				4·7s[3] (—N$^+$—C<u>H</u>$_3$)	1,610	282(2,850)
10	8·98	8·4	5·0	6·3s[1] (Ar—C<u>H</u>—Ar)	3,100	220(39,500)
					1,625	274(1,660)
					1,590	310(1,250)
						323(2,500)
11	9·4*	8·8	6·15	3·4[3] (—N$^+$—C<u>H</u>$_3$)	3,340	220(52,000)
				2·1[3] (—C—C<u>H</u>$_3$)	1,645	279(3,850)
					1,610	325(5,300)
12	9·5	8·8	6·1	2·0s[3] (C—C<u>H</u>$_3$)	3,150	219(74,000)
				3·7s[6] (2 × OC<u>H</u>$_3$)	1,620	274 (8,040)
					1,585	308 (4,480)
						322(5,710)
13	10·2*	8·9	4·3	6·4s[1] (Ar—C<u>H</u>—Ar)	3,300	228 (55,000)
			broad	4·7s[3] (—N$^+$—CH$_3$)	1,640	277(3,490)
					1,600	338(6,240)
14	9·15	8·5	5·95	6·3s[1] (Ar—C<u>H</u>—Ar)	3,200	
					1,630	—
					1,590	

* Methiodide

$NaBH_4$ to **7**, which was shown to be identical with the material obtained by reduction of the vinylogous amide[14] (**8**). The structure of **9**, from cyclohexanone was proven by dehydration and dehydrogenation of it to the known[15] 4-phenylisoquinoline.

The interaction of aliphatic aldehydes and ketones with 4-lithioisoquinoline is the most straightforward method so far for the synthesis of 4-alkylisoquinoline derivatives. When 4-lithioisoquinoline was reacted with dimethylformamide or with N-formylmethylaniline, the yield of isoquinoline-4-aldehyde reached 70%. This method is now the best method of preparation of this aldehyde; previous preparations[11] were rather laborious. .



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EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured in EtOH solution and IR spectra refer to nujol mulls. NMR spectra were recorded using a Varian A60 spectrometer; chemical shifts are expressed in ppm downfield from TMS as internal standard.

General procedure for benzylation of 2-methyl-1,2-dihydroisoquinolines. 2-Methyl-1,2-dihydroisoquinoline, from isoquinoline methiodide (10 g), in ether (250 ml) was treated with equimolar quantities of the benzyl bromide and Et_3N dissolved in EtOH (100 ml). The soln was heated under reflux for 4 hr under N_2, the ether being slowly replaced by EtOH. AcOK (4 g) was introduced and a soln of I_2 in warm EtOH added dropwise until the I_2 colour persisted. Refluxing was continued for 30 min. After cooling, excess I_2 was destroyed with SO_2 and the volume of the soln reduced to ca. 30 ml. Water, (100 ml), was then added and the mixture quickly extracted with $CHCl_3$ (3 × 50 ml). Evaporation of the combined, dried $CHCl_3$ extracts gave a red gum which crystallized on trituration with EtOH or acetone. Recrystallization was usually carried out with EtOH. The relevant data are collected in Tables 1 and 2.

2-Methyl-4-benzyl-6,7-dimethoxyisoquinolinium iodide. 6,7-Dimethoxyisoquinoline methodide was reduced with LAH in THF. The benzylation of the resulting 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline was performed as described above. The yield of 2-methyl-4-benzyl-6,7-dimethoxyisoquinolinium iodide, m.p. 214–215° (from EtOH) was 48·0%. (Found: C, 53·9; H, 4·8; N, 3·1; I, 30·8. $C_{19}H_{20}NO_2I$ requires: C, 54·2; H, 4·75; N, 3·3; I, 30·2%).

Preparation of 4-bromoisoquinoline. A mixture of isoquinoline (200 gm) and HBr (48%, 180 ml) was evaporated to dryness, Br_2 (80 ml) was added to the resulting white solid, and the mixture was heated under reflux so that HBr was allowed to escape. On cooling, the brick-red solid was basified (30% NaOH) and steam distilled. After a forerun of 1·23 g isoquinoline + 4-bromoisoquinoline, pure 4-bromoisoquinoline was collected as a white solid m.pt. 40°, total yield = 90 gms = 28%.

General procedure for alkylation of 4-lithioisoquinoline. A soln of n-BuLi in ether (50 ml) was prepared under N_2 from finely cut Li (0·45 gm) and n-BuBr (4·0 ml) as previously described, and cooled in an acetone-dry ice bath to an internal temp of −60° to −70°. 4-Bromoisoquinoline (5 g) was added portionwise; the soln slowly changed to a bright yellow colour. After stirring for 15 min 0·025 mole of the carbonyl compound in ether (50 ml) was added. The whole was then allowed to warm up to room temp, after which the complex was destroyed by the addition of water. At this point, many of the tertiary alcohol products

precipitated. In other cases, the ether layer was extracted with acid (2NHCl 3 × 50 ml), the acid layer was then basified (2N NH_4OH) and extracted with ether (3 × 50 ml). The ether extract was washed, dried ($MgSO_4$) and evaporated to give a dark red oil which solidified when triturated with petrol. The resulting bases were then purified by recrystallization, usually from a petrol fraction. In cases where the free base was difficult to isolate, the red oil from above was treated with either iodomethane or acetic anhydride to give the base methiodide or alcohol acetate respectively. Results are collected in Tables 3 and 4.

Preparation of isoquinoline-4-aldehyde. 4-Lithioisoquinoline was prepared from 4-bromoisoquinoline (5 g) and BuLi as detailed above, when N,N-dimethylformamide (2·0 ml) in ether (30 ml) at −60° was added. The mixture was allowed to warm to room temp, after which the complex was decomposed with water. The organic layer was separated and shaken vigorously with an equal volume of sat $NaHSO_3$ aq. The ppt was filtered off and washed with ether to remove organic matter and then added to an excess of 10% Na_2CO_3 aq. The resulting fluffy white solid was collected and recrystallized from water to give 2·55 g (68%) of isoquinoline-4-aldehyde m.p. 103°. (Lit. 103–104°C) λ_{max} (ε)nm 219(37,300) 285(3350), 322(4780) ν_{max} cm^{-1} 2750, 1690 (—CHO) 1620 (C=N—); NMR ($CDCl_3$), 10·4[1] (—CHO), 9·3[1] ($—C_1—\underline{H}$), 8·9[1] ($—C_3—\underline{H}$), 8·3–7·5 m[4] (remaining aromatic protons). (Found: C, 76·1; H, 4·7; N, 8·7. Cal'd. for $C_{10}H_7NO$: C, 76·4; H, 4·5; N, 8·9%).

4-Benzoylisoquinoline. A soln of the product obtained from 4-lithioisoquinoline and benzaldehyde (1·0 g) in $CHCl_3$ (50 ml) was stirred at room temp with MnO_2 (2·0 g) for 24 hr. The MnO_2 was removed, and the filtrate was evaporated to leave a pale red oil which crystallized from petrol (40–60°) as silky needles (0·83 g; 84%), m.p. 74–75°. 4-Benzoylisoquinoline has[12,13] m.p. 76–78°.

4-Phenylisoquinoline. A soln of the product obtained from 4-lithioisoquinoline and cyclohexanone (0·5 g) in decalin (25 ml) was heated under reflux for 5 hr with 10% Pd–C (100 mg). After cooling and filtering, the soln was extracted with 2N HCl (2 × 20 ml), and the acid extract was washed with ether, basified (NH_3) and extracted with ether (2 × 50 ml). The combined ethereal extracts were washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated to leave a pale red oil which slowly solidified to an off-white solid m.p. 63°, yield: 52%. The picrate was crystallized from EtOH, m.p. 209–210°, (Lit.[15] m.p. 209°). (Found: C, 57·9; H, 4·0; N, 12·9. Cal'd. for $C_{21}H_{14}N_4O_7$: C, 58·1; H, 3·25; N, 12·9%).

Acknowledgement—We wish to thank Allen & Hanbury Ltd. for a Research Studentship (to R. D. J. Clipperton) and M. N. Palfreyman for some experimental assistance.

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THE PREPARATION OF SOME BENZO[a]QUINOLIZINES, DIBENZO[a,h]QUINOLIZINES AND DIBENZO[a,f] QUINOLIZINES

(Tetrahedron, 1970, 26, 4985)

Tetrahedron. Vol. 26, pp. 4985 to 4994. Pergamon Press 1970. Printed in Great Britain

THE PREPARATION OF SOME BENZO[*a*]QUINOLIZINES, DIBENZO[*a,h*]QUINOLIZINES AND DIBENZO[*a,f*]QUINOLIZINES

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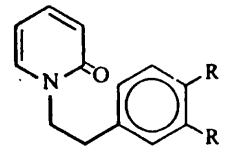
Abstract—Some further clarifications and corrections to the literature concerning the reactions between $POCl_3$ and certain heterocyclic amides are presented.

IN A previous paper[1] we confirmed earlier reports[2] that 1-β-arylethyl-2-pyridones (**1**) are not cyclized by $POCl_3$ to benzo[*a*]quinolizines (**2**) as originally reported by Sugasawa *et al.*,[3] and we also found that the reaction of 2-β-arylethylisocarbostyrils (**3**) with $POCl_3$ leads to the 1-chloro-2-β-arylethylisoquinolinium salts and not to the dibenzo[*a,h*]quinolizine structures (**4**).



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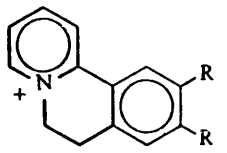

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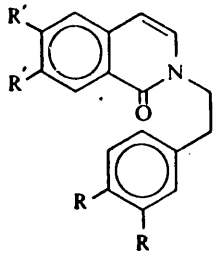

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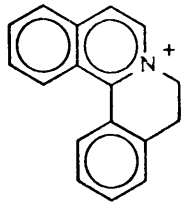
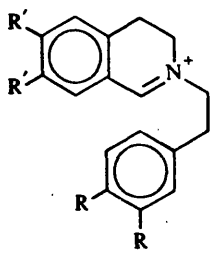


4

It was with some interest that we learned of the claim[4] that during the formation of the 3,4-dihydroisoquinolinium salts **5**, (R = OMe, R′ = H and R = R′ = OMe) from the 3,4-dihydroisoquinolines and β-3,4-dimethoxyphenethyl bromide, small amounts of **6** (R = OMe, R′ = H and R = R′ = OMe) respectively were formed, particularly when the structural proof rested upon a comparison of the basic material with that obtained by Sugasawa and Kakemi.[5] Repetition[6] of the reactions as described[4] confirmed our suspicions that the basic products are not the dibenzo[*a,h*]-quinolizine products (**6**), but the tetrahydroisoquinolines **7**, (R = OMe, R′ = H and

R = R′ = OMe) respectively, formed, presumably by disproportionation of the salts **5**. The fully aromatic compounds **8** (R = OMe, R′ = H and R = R′ = CMe) were also isolated.



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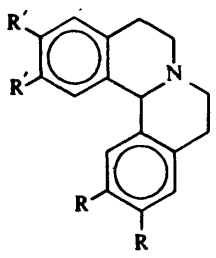

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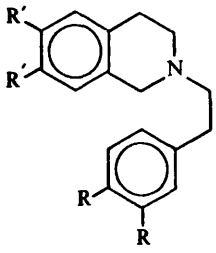

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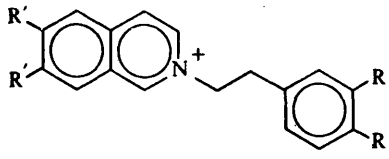

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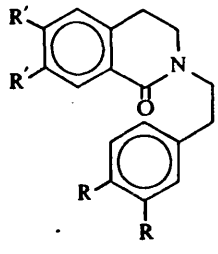

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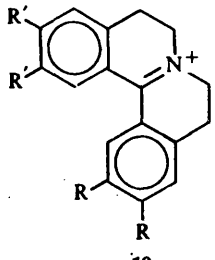
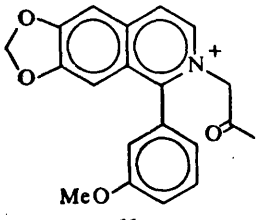


10

It has been reported[5] that oxidation of **5** (R = R′ = OMe) yields the dihydroisocarbostyril **9** (R = R′ = OMe) which, with $POCl_3$ is cyclized to **10** (R = R′ = OMe), but we were able to show[1] that **9** (R = R′ = OMe) is not formed under the conditions used[5] and that the "cyclization" product is simply the tetrahydroisoquinoline **7**, (R = R′ = OMe). We have now[6] found that the dihydroisocarbostyril **9**, (R = R′ = OMe) can be prepared by the hydrogenation of the corresponding isocarbostyril **3**, (R = R′ = OMe). When **9** (R = R′ = OMe) is treated with $POCl_3$ under the usual conditions, a quaternary salt, characterized as the iodide, m.p. 222° is produced in 34% yield. The structure **10** (R = R′ = OMe) follows from analytical and spectral data. The NMR spectrum (measured in CD_3SOCD_3 soln) is, due to the symmetry of the molecule about the $>C=N^+<$ grouping, particularly simple; two singlets at 3·8 and 4·0 δ are attributed to the four OMe groups, whilst the aromatic protons resonate as two two-hydrogen singlets at 7·3 and 7·34 δ. When **10** (R = R′ = OMe)

was reduced with $NaBH_4$, 2,3,11,12-tetramethoxy-5,6,8,9-tetrahydro-13 H-dibenzo-[a,h]quinolizine (**6**, R = R′ = OMe) was formed. The entire sequence of reactions was repeated with **3** (R = OMe, R′ = H), leading ultimately to **6** (R = OMe, R′ = H) in good overall yield. The parent dihydroisocarbostyril (**9**, R = R′ = H) could not be cyclized with $POCl_3$, thus confirming an earlier observation of Perkin,[7] who prepared **9** (R = R′ = H) by the electrolytic reduction of N-β-phenethylhomophthalimide.

Remarkably few syntheses of the dibenzo[a,h]quinolizine skeleton have appeared in the literature, although Bradsher *et al.*[8] have developed a successful route from 1-arylisoquinolines such as **11**.



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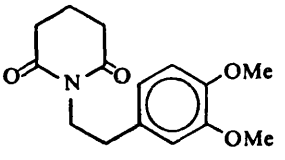

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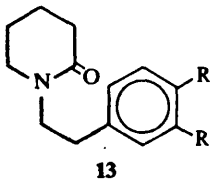

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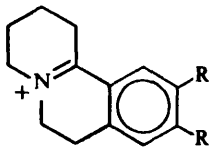

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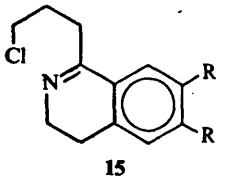

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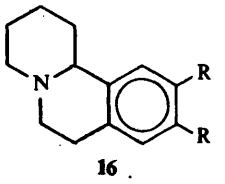


16

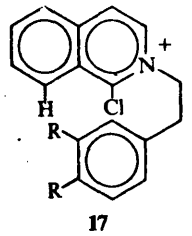
In 1939 Sugasawa *et al.*[9] reported that the N-β-arylethylpiperidone **13**, (R = OMe), obtained from the lactam **12**, is cyclized by $POCl_3$ to the benzo[a]quinolizine derivative **14** (R = OMe). The same product had previously[10] been prepared from **15** (R = OMe). Both groups of workers reduced their quaternary salts **14** to a base **16** (R = OMe), but there is some discrepancy in the descriptions of this material. We have now prepared **13** (R = OMe) by catalytic hydrogenation of the pyridone **1** (R = OMe), and have reacted it with $POCl_3$, thus obtaining a quaternary salt, isolated as the iodide, m.p. 206–207° (60% yield). Analytical and spectral data confirm that a cyclization to **14** (R = OMe) had occurred. Reduction of this product with $NaBH_4$ gave a gum the hydrochloride, picrate and methiodide of which closely resemble the salts described by Childs and Pyman[10] for their sample of **16** (R = OMe). We have repeated the entire reaction sequence from **1** (R,R = CH_2O_2), and **16** (R,R = CH_2O_2) has been obtained in good yield. As expected, the parent piperidone **13**, (R = H) was not cyclized by $POCl_3$, but when it was treated with PPA a small

amount of a quaternary salt was isolated which, when reduced with $NaBH_4$, yielded a base **16** (R = H) identical with that obtained from **15** (R = H).

There are numerous cyclization reactions of amides reported in the literature, especially by the Japanese workers and we chose to re-examine the quinoline series. It has been shown[11] that, although the reactivities of 1-chloroisoquinolinium salts and 2-chloroquinolinium salts towards nucleophiles are about the same, each is much more susceptible than 2-chloropyridinium ions to such reagents. However, it is possible that with ions such as **17** there is some steric repulsion to the approach of the bulky aromatic ring, but this should be absent in the quinolinium salt **18**.

The previously reported[12] reaction between the carbostyril **19** (R = H) and $POCl_3$ was repeated under the original conditions and a quaternary iodide was isolated, m.p. 180–181° (dec). Akahoshi reports m.p. 185–186°. Elemental analysis of our sample indicated the presence of both chlorine and iodine, but a better analytical derivative was obtained when ethanolic $HClO_4$ was added to an ethanol solution of the iodide. The product was identified as **20** (R = H, R′ = OEt, $X = ClO^{4-}$) by elemental and spectral analysis. Clearly the iodide m.p. 180–181° is **20** R = H, R′ = Cl, X = I) and not the ring-closed material **21** (R = R′ = H) as claimed by Akahoshi. Further evidence for structure **20** was secured by showing that the product obtained from it by hydrogenation is identical with **22** (R = H) obtained by the hydrogenation of **18** (R = H).

When **19** (R,R = CH_2O_2) was similarly reacted with $POCl_3$ a quaternary iodide m.p. 187–189° was obtained, together with large proportions of **19** (R,R = CH_2O_2). Our analytical data are compatible with structure **20** (R,R = CH_2O_2, R′ = Cl, X = I) rather than the dibenzo[*a,f*]quinolizine **21**,(R,R = CH_2O_2, R′ = H) claimed by the Japanese workers. However, a second compound, m.p. 296–298° (d) was isolated from the reaction mixture by us to which we allocate the structure **21** (R,R = CH_2O_2, R′ = H), once again from the spectral data. The peak at highest *m/e* ratio in the mass spectrum of the compound corresponds to an ion of structure **23**; dehydrogenation of **21** (R,R = CH_2O_2, R′ = H) under these conditions is not surprising. Reduction of **21** (R,R = CH_2O_2, R′ = H) gave a base **24**, m.p. 128°, which was shown NOT to be identical with **22** (R,R = CH_2O_2) obtained by the reduction of **18** (R,R = CH_2O_2).



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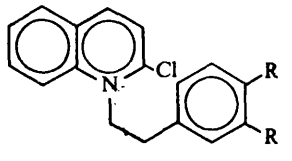

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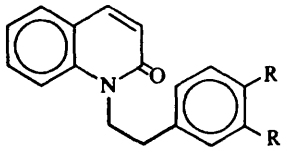

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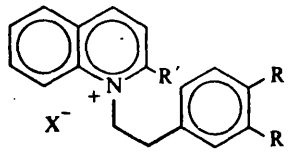
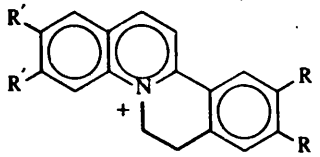


20

TABLE 1

Compound	m.p.	Mol. formula	% Yield	Analysis % Found C	H	N	Br	I	% Required C	H	N	Br	I
A	143–144°	$C_{13}H_{14}BrN$	85	59·2	5·5	5·2	30·1	—	59·1	5·3	5·3	30·25	—
B	194–196°	$C_{15}H_{18}BrNO_2$	70	55·35	5·7	4·2	24·9	—	55·6	5·6	4·3	24·65	—
C	227–228°	$C_{14}H_{14}BrNO_2$	68	54·4	4·5	4·5	26·0	—	54·6	4·6	4·5	25·9	—
1, R = H	103–105°	$C_{13}H_{13}NO$	75	78·6	6·8	6·8	—	—	78·3	6·6	7·0	—	—
1, R = OCH_3	78–79°	$C_{15}H_{17}NO_3$	60	69·55	6·75	5·7	—	—	69·5	6·6	5·4	—	—
1, RR = —OCH_2O—	145–147°[c]	$C_{14}H_{13}NO_3$	65	69·3	5·5	5·7	—	—	69·1	5·4	5·8	—	—
13, R = H	39–42°[c]	$C_{13}H_{17}NO$	95	76·7	8·6	6·8	—	—	76·8	8·4	6·9	—	—
13, R = OCH_3		$C_{15}H_{21}NO_3$	90	68·5	7·9	5·5	—	—	68·4	8·0	5·3	—	—
13, RR = —OCH_2O—	93–96°[c]	$C_{14}H_{17}NO_3$	95	68·2	6·9	5·7	—	—	68·0	6·9	5·7	—	—
14, R = H	173–174°[c]	$C_{13}H_{16}IN$	17	49·4	5·1	4·7	—	40·2	49·8	5·15	4·5	—	40·5
14, R = OCH_3	206–207°[c]	$C_{15}H_{20}INO_2$	56	47·3	5·3	3·4	—	33·2	47·4	5·9	3·45	—	33·3
14, RR = —OCH_2O—	216–220°[c]	$C_{14}H_{16}INO_2$	15	46·4	4·2	3·7	—	36·1	47·1	4·5	3·9	—	35·5
16, R = H	241–243°[c]	$C_{13}H_{17}N.HCl$	70	69·8	8·0	6·7	15·8	(Cl)	69·8	8·1	6·3	15·8	(Cl)
16, R = OCH_3	243–244°[c]	$C_{15}H_{21}NO_2.CH_3I$	55	49·6	6·25	3·4	—	32·9	49·6	6·2	3·6	—	32·6
16, R = OCH_3	232–233°	$C_{15}H_{21}NO_2.HCl$	68	63·3	7·7	4·9	12·8	(Cl)	63·5	7·8	4·9	12·5	(Cl)



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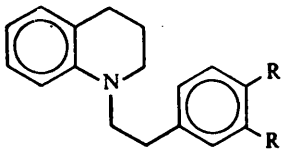

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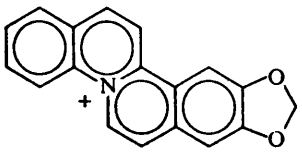

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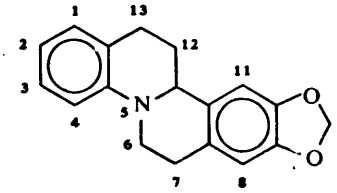

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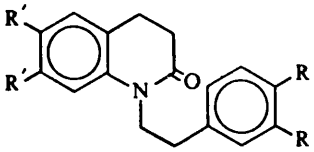

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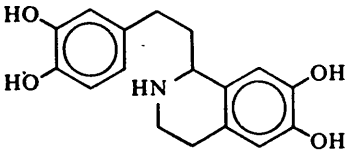

26

The dihydroquinolone (25, RR = CH_2O_2, R′ = H), when reacted with $POCl_3$, gave the same product **21** (RR = CH_2O_2, R′ = H) as that obtained from **19** (RR = CH_2O_2). Sugasawa *et al.*[13] had previously shown that the product obtained from **25** (R = R′ = OMe) and $POCl_3$ was **21**, (R = R′ = OMe), this latter structure is secure by its alternative synthesis[14] from **26** via phenolic coupling and methylation.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

The reaction between 3,4-dihydroisoquinoline and β-(3,4-dimethoxyphenyl)ethyl bromide

The isoquinoline (1·8 g) and the bromide (1·8 g) were heated together for ¾ hr at 145°. The reaction mixture was triturated with hot benzene (2 × 25 ml) and the decanted benzene soln extracted with dil HCl. The acidic extract was made alkaline with 10% NaOHaq and the liberated base obtained as a brown oil by extraction with ether and evaporation of the dried extracts. The hydrochloride of the base was obtained by passing HCl gas through a soln of the base in ether. Recrystallization of the white solid so obtained yielded *2-β-(3,4-dimethoxyphenyl)ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride* (7, R′ = H, R = OMe) (0·45 g, 18%) as colourless prisms m.p. 218–219° (Lit[4] m.p. 212–214°) (Found: C, 68·35; H, 7·2; N, 4·3. $C_{19}H_{24}ClNO_2$ requires: C, 68·4; H, 7·2; N, 4·2%) [This material is identical in all respects with an authentic sample prepared by reduction of **5**, (R = H, R′ = OCH_3) with sodium borohydride.]

The residual solid after trituration was dissolved in hot water (40 ml) and the mixture filtered through Kieselguhr. The soln was made just alkaline (pH 8) with $NaHCO_3$aq and treated with a slight excess of 10% NaCNaq to precipitate the 3,4-dihydroisoquinoline as its pseudocyanide. The solid was filtered and to the filtrate was added a few drops of 60% $HClO_4$ when a small amount of a yellow oil separated. Treatment of the oil with acetone produced a yellow solid which was crystallized from EtOH to give *2-β-(3,4-dimethoxyphenyl)ethyl-isoquinolinium* (**8**, R′ = H, R = OMe) perchlorate (70 mg) as yellow needles m.p. 213–214. This material is identical in all respects with an authentic sample prepared by treating **8** as its bromide salt in EtOH with 60% $HClO_4$.

The reaction between 6,7-*dimethoxy*-3,4-*dihydroisoquinoline and* β-(3,4-*dimethoxyphenyl*)*ethyl bromide*

A similar procedure to the above using the isoquinoline (4·1 g), the bromide (4·7 g) and a 50% $CHCl_3$: benzene soln as triturant yielded 2β-(3,4-*dimethoxyphenyl*)*ethyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline hydrochloride* (7, R′ = R = OCH_3) as white needles (0·3 g) m.p.[1] 233–234 also isolated from the reaction was 2-β-(3,4-dimethoxyphenyl)ethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide, m.p. 199–201° and a small quantity of the fully aromatic isoquinolinium iodide, m.p. 183–184°. Both of these compounds were compared with authentic specimens, with which they were found to be identical.

Preparation of the dibenzo[a,h]*quinolizinium salts*

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-3,4-*dihydroisocarbostyril* (9, R′ = H, R = OCH_3) was prepared by treatment of the corresponding isocarbostyril 3, (2·2 g) in MeOH (100 ml) with Raney Ni (0·25 g) and H_2 (1350 lbs/sq in) at 150° for 2 hr. Evaporation of the filtered (Kieselguhr) reaction mixture yielded a solid which on recrystallization from EtOH gave 9 (R′ = H, R = OCH_3) as long colourless needles (2·2 g), m.p. 109–110°; λ_{max} (ε)nm, 231 (13,900, 281 (4,400); ν_{max} cm^{-1}, 1637, 1613, 1602; NMR ($CDCl_3$) ppm, 2·7–3·0 (4H, m) and 3·2–3·9 (4H, m), (methylenic protons); 3·8 (6H, s), (2x-OCH_3); 6·8 (3H, s), (C_6H_3≡); 7·1–7·45 (3H, m), (—C_5H, —C_6H, —C_7H,; 8·1 (1H, q), (—C_8H). (Found: C, 73·3; H, 6·5; N, 4·3 $C_{19}H_{21}NO_3$ requires: C, 73·3; H, 6·8; N, 4·5%).

Similarly prepared were

(a) 2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6,7-*dimethoxy*-3,4-*dihydroisocarbostyril* (9, R′ = R = OCH_3) as colourless needles (96%), m.p. 128–129° from EtOH/pet. ether (60–80°); λ_{max} (ε)nm, 273 (8,500), 299 (6,800). ν_{max} cm^{-1}, 1644, 1600, 1589; NMR ($CDCl_3$) ppm, 2·4–3·1 (6H, m) and 3·4 (2H, m), (methylenic protons); 3·85 (6H, s) and 3·90 (3H, s) and 3·95 (3H, s), (4x —O CH_3); 6·6 (1H, s), (—C_5H); 6·8 (3H, s), (C_6H_3≡); 7·66 (1H, s), (—C_8H). (Found: C, 67·7; H, 7·2; N, 3·75. $C_{21}H_{25}NO_5$ requires: C, 67·9; H, 6·8; N, 3·8%).

(b) 2-β-*Phenylethyl*-3,4-*dihydroisocarbostyril* (9, R′ = R = H) as colourless prisms (98%) from EtOH/light petroleum (60–80°) m.p. 76–77° (Lit.[7] m.p. 77–78°); λ_{max} (ε)nm, 230 (15,000), 252 (11,200), 264 sh (8,800), 279 sh (4,100); NMR ($CDCl_3$) ppm, 2·80 (2H, t, J = 6·0 Hz) and 2·92 (2H, t, J = 7·5 Hz), (2x $ArCH_2$—); 3·32 (2H, t, J = 6·0 Hz) and 3·77 (2H, t, J = 7·5 Hz), (2x—CH_2N=); 7·1–7·4 (3H, m), (—C_5H, —C_6H and —C_7H); 7·26 (5H, s), (C_6H_5—); 8·1 (1H, m), (—C_8H). (Found: C, 81·0; H, 6·9; N, 5·6. Calc. for $C_{17}H_{17}NO$: C, 81·2; H, 6·8; N, 5·6%).

2,3-*Dimethoxy*-5,6,8,9-*tetrahydrodibenzo*[a,h]*quinozinium iodide* (10, R′ = H, R = OCH_3) was obtained by heating on an oil bath, at 130°, for 2½ hr, a mixture of 9 (R′ = H, R = OCH_3), (1·1 g) and $POCl_3$ (7 ml). The cooled mixture was shaken with successive portions (15 ml) of light petroleum (60–80°), the residue dissolved in water, the soln extracted with benzene (15 ml) and filtered (Kieselguhr). Addition of aqueous KI precipitated a pure yellow solid (1·25 g). Recrystallization from EtOH yielded the quaternary iodide m.p. 215–216° as yellow prisms; λ_{max} (ε)nm, 268 (13,700), 298 (11,800), 317 (11,300), 388 (8,300); ν_{max} cm^{-1}, 1619, 1600, 1557, 1517; NMR (DMSO.D_6) ppm, 3·0–3·4 (4H, m), ($ArCH_2$—); 3·5–4·3 (4H, m), (2x—CH_2N≡); 3·8 (3H, s), (—OCH_3); 4·0 (3H, s), (—OCH_3); 7·17 (1H, s), (—C_4H); 7·33 (1H, s), (—C_1H); 7·7 (4H, m), (—$C_{10}H$, —$C_{11}H$, —$C_{12}H$, —$C_{13}H$). (Found: C, 54·0; H, 4·7; N, 3·5; I, 30·2. $C_{19}H_{20}NO_2I$ requires: C, 54·2; H, 4·8; N, 3·3; I, 30·1%).

2,3,11,12-*Tetramethoxy*-5,6,8,9-*tetrahydrodibenzo*[a,h]*quinolizinium iodide* (10, R′ = R = OCH_3) was similarly prepared from the corresponding amide (1·7 g) as yellow rosettes (0·75 g) from MeOH m.p. 221–222°; ν_{max} cm^{-1}, 1604, 1568, 1552, 1524. NMR (DMSO.D_6), 3·0–3·5 (4H, m) (2x $ArCH_2$—); 3·8–4·2 (4H, m); (2x —CH_2N≡); 3·83 (6H, s), (2x —OCH_3); 4·0 (6H, s), (2x —OCH_3); 7·28 (2H, s), (—C_4H, —$C_{10}H$); 7·34 (2H, s), (—C_1H, —$C_{13}H$). (Found: C, 52·1; H, 5·5; N, 2·8; I, 25·8. $C_{21}H_{24}INO_4$ requires: C, 52·4; H, 5·0; N, 2·9; I, 26·4%).

The parent compound 10 (R′ = R = H) could not be prepared by this procedure. Reduction of the salts 10 under normal conditions with sodium borohydride yielded:

(a) 2,3-*Dimethoxy*-5,6,8,9-*tetrahydro*-13bH-*dibenzo*[a,h]*quinolizine* (6, R′ = H, R = OCH_3) as a white solid (93·5%) m.p. 126–127° which was characterized as its hydrochloride (ppted from a soln of the base in dry ether by anhyd HCl) m.p. 227–228° from EtOH as small colourless needles; ν_{max} cm^{-1}, 2300, 1610, 1515; NMR ($CDCl_3$) ppm, 1·9 (4H, m) (2x $ArCH_2$—), 3·0–3·5 (5H, m), (=NH and 2x —CH_2N≡); 3·79 (3H, s) and 3·81 (3H, s), (2x —OCH_3), 5·53 (1H, s), (13b —H); 6·67 (1H, s), (—C_4H), 6·77 (1H, s), (—C_1H); 7·2–7·5 (4H, m), (—$C_{10}H$, —$C_{11}H$, —$C_{12}H$, —$C_{13}H$). (Found: C, 68·6; H, 6·7; N, 4·3; Cl, 11·0. $C_{19}H_{22}ClNO_2$ requires: C, 68·75; H, 6·7; N, 4·2; Cl, 10·7%). The methiodide was obtained as small yellow needles from acetone m.p. 242–243°. (Found: C, 54·7; H, 5·5; N, 3·0; I, 29·3. $C_{20}H_{24}INO_2$ requires: C, 54·9; H, 5·5; N, 3·2; I, 29·0%).

(b) 2,3,11,12-*Tetramethoxy*-5,6,8,9-*tetrahydro*-13b*H*-*dibenzo*[a,h]*quinolizine* (**6**, R′ = R = OCH_3) as white crystals (95%) m.p. 161–162°. The hydrochloride gave colourless prisms from EtOH m.p. 225–226°; ν_{max} cm^{-1} 2500, 2350, 1609, 1511; NMR ($CDCl_3$) ppm, 2·8–3·8 (8H, m), 3·78 (6H, s, 2x $OC\underline{H}_3$); 3·89 (6H, s), (2x $OC\underline{H}_3$); 5·54 (1H, s), (—C(—H)—); 6·72 (2H, s), (C_4H and C_{10}H); 6·77 (2H, s), (—C_1H, —C_{13}H). (Found: C, 64·2; H, 6·2; N, 3·6; Cl, 9·1. $C_{21}H_{26}ClNO_4$ requires: C, 64·7; H, 6·2; N, 3·6; Cl, 9·1%).

Preparation of the benzo[a]*quinolizines*

The pyridinium salts A, B and C* were prepared by heating, for 8 hr, a soln of the appropriate β-phenethylbromide (1 mole) in dry acetone and pyridine (3 mole). After cooling the solid colourless products were collected and recrystallized from EtOH.

*A = 1-β-*Phenylethylpyridinium bromide*; B = 1-β-(2,3-*dimethoxyphenyl*)*ethyl pyridinium bromide*; C = 1-β-(2,3-*methylenedioxyphenyl*)*ethyl pyridinium bromide.*

Preparation of the 2-*pyridones*

1-(β-*Phenylethyl*)-2-*pyridone* (**1**, R = H) was prepared by the method of Sugasawa[5] (Table 1).

1-[β-(2,3-*Dimethoxyphenyl*)*ethyl*]-2-*pyridone* (**1**, R = OCH_3) was prepared by treating a soln of A (13·6 g) in water (50 ml) rapidly with a soln $K_3Fe(CN)_6$ (60 g) in water (140 ml) under N_2. The dark soln was stirred for ½ hr. KOH (73 g) in water (60 ml) was then added dropwise so that the temp of the soln remained below 40°. After the addition the temp was raised to 65° for 1 hr after which time the cooled reaction mixture was shaken with benzene (200 ml), filtered and the aqueous phase separated and further extracted with benzene (2 × 100 ml). The combined extracts were dried and on evaporation gave an oil which solidified on standing and was recrystallized from benzene: light petroleum (60–80°) (Table 1); λ_{max} (ε)nm, 230 (13,900), 287 (5,800), 306 (5,700); ν_{max} cm^{-1}, 1663, 1582, 1510; NMR (CF_3COOH), 3·1 (2H, t, J = 7·0 Hz), (Ar—CH_2—), 4·5 (2H, t, J = 7·0 Hz) (—CH_2N═); 3·75 (6H, s), (2 × —OCH_3); 6·5 (3H, s), (C_6H_3≡); 6·5–8·0 (4H, m), (C_6H_4═).

1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-2-*pyridone* (**1**, R, R = —OCH_2O—) was prepared and recrystallized by the above method (Table 1). ν_{max} cm^{-1}, 1665, 1582.

Preparation of the piperidones

The piperidones were prepared by reduction of the corresponding pyridones (2·0 g) in MeOH (100 ml) over Raney Ni (0·25 g) at 85 atms and 140°. After filtration and evaporation oily products were obtained which solidified on standing, these were recrystallized from benzene: light petroleum (60–80°) mixtures (Table 1) to give

(a) 1-(β-*Phenylethyl*)-2-*piperidone* (**13**, R = H), ν_{max} cm^{-1}, 1647, 1488, 747, 695. NMR ($CDCl_3$) ppm, 1·65 (4H, m), (—CH_2CH_2— at C_4 and C_5); 2·3 (2H, broad s), (—$C\underline{H}_2$CO—); 2·9 (2H, t, J = 7·0 Hz), (Ph—$C\underline{H}_2$—); 3·1 (2H, broad s) (—CH_2N—); 3·5 (2H, t, J = 7·0 Hz), (PhC$H_2C\underline{H}_2$—); 7·23 (5H, s), (C_6H_5—).

(b) 1-[β-(3,4-*Dimethoxyphenyl*)*ethyl*]-2-*piperidone* (**13**, R = OCH_3). ν_{max} cm^{-1}, 1620, 1587, 1508; NMR ($CDCl_3$) ppm, 1·6 (4H, m), (—CH_2CH_2— at C_4 and C_5), 2·2 (2H, broad s), (—$C\underline{H}_2$CO—); 2·6 (2H, t, J = 7·0 Hz), (ArCH_2—); 2·9 (2H, broad m), (—CH_2N═); 3·3 (2H, t, J = 7·0 Hz), (Ar$CH_2C\underline{H}_2$N═); 6·4 (3H, s), (C_6H_3≡).

(c) 1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-2-*piperidone* (**13**, R, R = —OCH_2O—). ν_{max} cm^{-1}, 1616, 1500, 1480; NMR ($CDCl_3$) ppm, 1·7 (4H, m) (—CH_2CH_2— at C_4 and C_5); 2·35 (2H, m), (—CH_2CO—); 2·75 (2H, t, J = 7·5 Hz), (ArCH_2—); 3·1 (2H, m), (—CH_2N═); 3·5 (2H, t, J = 7·5 Hz) (Ar$CH_2C\underline{H}_2$N═); 5·9 (2H, s), (—O CH_2 O—) 6·7 (3H, s), (C_6H_3≡).

Preparation of the quinolizinium salts (**14**)[15]

(a) 1,2,3,4,6,7-*Hexahydrobenzo*[a]*quinolizinium iodide* (**14**, R = H) as a yellow crystalline solid from EtOH (Table 1). Picrate as dark brown needles from EtOH m.p. 137–139° (Lit.[15] 139–140°); ν_{max} cm^{-1}, 1663, 1602, 1570; NMR (DMSO.D_6) ppm, 2·3 (4H, m), (—CH_2CH_2— at C_2 and C_3); 3·2–3·4 (4H, m), (2 × CH_2— at C_1 and C_7); 4·0–4·2 (4H, m), (2 × —CH_2— N^+≡); 7·0–7·3 (4H, m), (C_6H_4═).

(b) 1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium iodide* (**14**, R = OCH_3) as brown shiny needles from EtOH (Table 1); λ_{max} (ε)nm, 246 (15,600), 304 (8,200), 355 (8,900); ν_{max} cm^{-1}, 1648, 1607, 1574, 1522; NMR ($CDCl_3$) ppm, 2·0 (4H, m) (—CH_2CH_2— at C_2 and C_3); 3·2 (4H, 2 × —CH_2— at C_1 and C_7); 3·9 (10H, broad s), (2 × —OCH_3 and 2 × —CH_2N^+≡); 6·65 (1H, s), (—C_8H); 7·0 (1H, s), (—C_{11}H).

(c) 1,2,3,4,6,7-*Hexahydro*-9,10-*methylenedioxybenzo*[a]*quinolizinium iodide* (**14**, R, R = —OCH_2O—) as yellow prisms from EtOH (Table 1); λ_{max} (ε)nm, 249 (14,700), 296 (7,800), 362 (6,900); ν_{max} cm^{-1}, 1648, 1603, 1500; NMR ($CDCl_3$) ppm, 2·0 (4H, broad s) (—CH_2CH_2— at C_2 and C_3); 3·02 (4H, broad s), (2 ×

—CH_2— at C_1 and C_7); 3·9 (4H, broad s), (2× —CH_2—$\overset{+}{N}\equiv$); 6·0 (2H, s), (—OCH_2O—); 6·6 (1H, s), (—C_8H); 7·0 (1H, s), (C_{11}—H).

Reduction of the benzoquinolizinium salts

Ethanolic solutions of the salts **14** were reduced by the addition of an excess of aqueous $NaBH_4$ in the usual way giving: (a) 1,2,3,4,6,7-*Hexahydro*-11bH-*benzo*[a]*quinolizine* (**16**, R = H) as an oil which was characterized as its *hydrochloride*; ν_{max} cm^{-1}, 2520, 2470, 1602. The Methiodide had a m.p. 226–229° from EtOH. (b) 1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine* (**16**, R = CH_3O) as a colourless gum which was characterized as its *methiodide*; ν_{max} cm^{-1} 1612, 1516, 1463.

1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-3,4-*dihydrocarbostyril* (**25**, R, R = —OCH_2O—).

The carbostyril, **19** (R,R = —OCH_2O—), (1·4 g) was hydrogenated as the pyridones **13** yielding the dihydro-compound (1·3 g) as colourless needles m.p. 92–93°; λ_{max} (ε)nm, 245 (7,700), 286 (3,700); ν_{max} cm^{-1}, 1665, 1657, 1600; NMR ($CDCl_3$) ppm, 2·5–3·0 (6H, m); 4·15 (2H, m), (—CH_2CO—; 5·94 (2H, s), (—OCH_2O—); 6·76 (3H, broad s), (≡C_6H_3); 7–7·25 (4H, m), (C_5C_6,C_7 and C_8 H's). (Found: C, 73·2; H, 5·9; N, 4·9; $C_{18}H_{17}NO_3$ requires: C, 73·2; H, 5·8; N, 4·7%).

The reaction of **19** (RR = —OCH_2O—) *with* $POCl_3$

A soln of the carbostyril (2·0 g) in $POCl_3$ (13 ml) was heated in an oil bath 2 hr at 140°. Excess $POCl_3$ was removed by distillation and the residue triturated with portions of light petroleum (60–80°), (15 ml). The residue was treated with warm water (2 × 30 ml) and insoluble material removed by filtration. The addition of KI precipitated a yellow solid (2·5 g). The crude product was divided into two. (i) The crude material (1·25 g) was triturated with several portions of warm EtOH and the residue (0·45 g) was 1-[β-(3,4-*methylenedioxyphenyl*)*ethyl*]-2-*chloroquinolinium iodide* (**20**, RR = —OCH_2O—, R′ = Cl) m.p. 187–189°; λ_{max} 242, 290, 332; ν_{max} cm^{-1}, 1610, 1582, 1569; NMR (CF_3COOH) ppm, 3·45 (3H, t, J = 7·5 Hz), ($ArCH_2$—); 5·6 (2H, t, J = 7·5 Hz), (=$\overset{+}{N}$—CH_2); 5·98 (2H, s), (—OCH_2O—); 6·78 (3H, m); 8·0–8·6 (4H, m), (C_5,C_6,C_7,C_8-H's); 8·64 (2H, s), (C_3 and C_4-H's). (Found: Cl, 9·3; I, 25·8. $C_{18}H_{15}NO_2ClI$ requires: Cl, 8·1; I, 28·1%). (ii) The crude material (1·25 g) was dissolved in MeOH (25 ml) and filtered. On standing for some days the crystalline 9,10-*methylenedioxy*-6,7-*dihydrobenzo*[a,f]*quinolizinium iodide* (**21**, R,R = —OCH_2O—, R′ = H), (0·12 g) m.p. 296–298° d. separated; λ_{max} (ε)nm 257 (12,000), 290 (14,600), 342 (5,600), 414 (14,500); ν_{max} cm^{-1}, 1605, 1572; NMR (DMSO . D_6) ppm, 3·38, (2H, t, J = 7·0 Hz), (—C_7H_2—); 5·16, (2H, t, J = 7·0 Hz), (—C_6H_2—), 6·32 (2H, s), (—OCH_2O—); 7·3, (1H, s), (C_8H); 7·63–8·82, (5H, m), (C_1, C_2, C_3, C_4 and C_{13}Hs). 8·06, (1H, s) (C_{11}-H), 9·23 (1H, d, J = 9·0 Hz), (C_{12}-H). (Found: C, 53·8; H, 3·2; N, 3·3; I, 31·7. $C_{18}H_{14}INO_4$ requires: C, 53·6; H, 3·5; N, 3·5; I, 31·5%); M/S (70 eV). P. m/e = 401. Starting material **9** (RR = —OCH_2O—), (1·2 g) was recovered from the combined mother liquors of (i) and (ii).

The reaction of **25** (RR = —OCH_2O—) *with* $POCl_3$

The dihydrocarbostyril (0·9 g) was treated with $POCl_3$ in the usual way yielding 9,10-*methylenedioxy*-6,7-*dihydrodibenzo*[a,f]*quinolizinium iodide* (**21**; 0·65 g, 53%) m.p. 296–298° as yellow garnets from EtOH. This material was identical (IR, UV, NMR) with, and did not depress, on admixture, the m.p. of the salt m.p. 296–298° obtained from the previous reaction. 9,10-*Methylenedioxy*-6,7,12,13-*tetrahydro*-11b H-*dibenzo*-[a,f]*quinolizine* (**24**, RR = —OCH_2O—). To the corresponding quinolizinium salt **23**, (0·4 g) dissolved in 20% aqueous EtOH (20 ml) was added a soln (5 ml) of $NaBH_4$ in the same solvent. The stirred soln deposited a white solid (0·25 g) which crystallized from EtOH as small colourless prisms m.p. 132–133° which became yellow on exposure to air; λ_{max} (ε)nm 263 (9,300), 300 (6,100); ν_{max} cm^{-1}, 1605, 1568; NMR ($CDCl_3$) ppm, 2·0–3·3 (8H, m); 3·8 (1H, m), (C_{11b}-H); 5·93 (2H, s), (—OCH_2O—); 6·63 (1H, s), (C_8-H); 6·79 (1H, s), (C_{11}-H), 6·55–7·25 (4H, m), (C_1,C_2,C_3 and C_4-Hs). The methiodide was obtained from EtOH as bright yellow garnets m.p. 221–223°. (Found: C, 54·4; H, 4·5; N, 2·9; I, 30·1. $C_{19}H_{20}INO_2$ requires: C, 54·2; H, 4·8; N, 3·3; I, 30·1%).

1-[β-(3,4-*Methylenedioxyphenyl*]-1,2,3,4-*tetrahydroisoquinoline*. **18**, RR = —OCH_2O—) was reduced with $NaBH_4$ as in the previous case; no solid material separated from the reaction mixture. The usual dilution and extraction procedure yielded solid product (70%) which recrystallized from EtOH as clumps of needles m.p. 124–125°. A mixed m.p. determination carried out with the base obtained in the previous reduction reaction showed a marked depression; λ_{max} (ε)nm, 233 (16,400), 292 (3,500). ν_{max} cm^{-1}, 1610, 1580; NMR ($CDCl_3$) ppm, 2·6–3·6 (8H, m), 4·1 (2H, m), (Ar—CH_2—N=), 5·94 (2H, s), (—OCH_2O—), 6·77 (3H, s), (C_6H_3≡), 6·2–7·2 (4H, m), (C_6H_4=). (Found: C, 76·8; H, 7·1; N, 4·8. $C_{18}H_{19}NO_2$ requires: C, 76·8; H, 6·8; N, 5·0%).

The reaction of 1-β-*phenylethylcarbostyril* (**19**, R = H) *with* $POCl_3$

The literature method[12] was employed. From **19** (R = H: 0·7 g) yellow needles (0·6 g) m.p. 180–181° were obtained, and crystallized by the addition of ether (3 vol) to an ethanolic soln of the salt (1 vol). (Lit.[12] 185–186); λ_{max} (ε)nm, 247 (18,700), 331 (8,400); ν_{max} cm^{-1}, 1620, 1610, 1595; NMR (DMSO.D_6) ppm, 2·8 (2H, t, J = 7·5 Hz), (—C<u>H</u>$_2$Ar); 4·5 (2H, t, J = 7·5 Hz), (—CH_2—$\overset{+}{N}$≡) 6·65 (1H, d, J = 7·0 Hz); (C_4—H); 7·5 (5H, s), (C_6H_5—); 7·4, 7·8 (4H, m). (C_6H_4=); 7·95 (1H, d, J = 7·0 Hz), (—C_3H). (Found: Cl, 5·95; I, 44·8. $C_{17}H_{15}I$ NCl requires: Cl, 9·0; I, 32·1%). A soln of the iodide in a minimum of EtOH was treated with a few drops of 60% $HClO_4$, and 2-*ethoxy*-1-β-*phenylethylquinolinium perchlorate* (**20**, R = H, R′ = —OCH_2CH_3, X = ClO_4) crystallized as grey needles m.p. 209–210°; NMR (DMSO.D_6) ppm, 1·5 (3H, t, J = 8·0 Hz), (<u>C</u>H$_3$CH$_2$—); 3·2 (2H, t, J = 7·5 Hz), (ArCH$_2$—); 4·7 (2H, q, J = 8·0 Hz), (CH_3C<u>H</u>$_2$—); 5·0 (2H, t, J = 7·5 Hz), (—CH_2—N≡); 7·35 (5H, s), (C_6H_5—); 7·6–8·5 (4H, m), (C_6H_4=); 7·9 (1H, d, J = 7·0 Hz), (—C_3H); 9·15 (1H, d, J = 7·0 Hz), (—C_4H). (Found: C, 58·0; H, 5·15; N, 3·85; Cl, 9·85. $C_{19}H_{20}Cl$ NO_5 requires: C, 60·5; H, 5·3; N, 3·7; Cl, 9·6%).

The catalytic reduction of **20** (R = H, R′ = Cl, X = I) *and* (R = R′ = H, X = Br)

The quaternary salt (1·0 g) dissolved in air free EtOH (200 ml) was reduced in the presence of Adams catalyst at 45 lb/sq in for 16 hr. The catalyst was filtered off, the filtrate evaporated to low bulk and a few drops of conc HI aq added to it. On standing EtOH soln from the reduction of bromide salt deposited the hydroiodide of 1-β-*phenylethyl*-1.2.3.4-*tetrahydroquinoline* (**22**, R = H) as pale yellow cubes (0·6 g) m.p. 209–211°; λ_{max} (ε)nm, 266 (1,050); ν_{max} cm^{-1}, 2730, 2680, 1600, 750, 710. The EtOH soln obtained by reduction of the chloro-iodide salt deposited pale yellow cubes (0·2 g) m.p. 208–210°, identical in all respects with the authentic 1-β-phenylethyl-1,2,3,4-tetrahydroquinoline hydroiodide.

Acknowledgement—We thank Mr. R. A. Mason, an undergraduate of this Department, for the experiments with **19**, (R = H and RR = CH_2O_2).

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1,2-DIHYDROISOQUINOLINES - REARRANGEMENT III

(Tetrahedron, 1970, 26, 5265)

Tetrahedron. Vol. 26, pp. 5265–5274. Pergamon Press 1970. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XV[1]

REARRANGEMENT III

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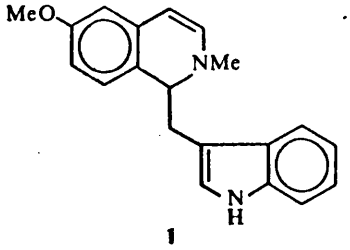
Abstract—The acid-catalysed rearrangement of a 1-allyl-1,2-dihydroisoquinoline into a 3-allyl-3,4-dihydroisoquinolinium salt has been shown to occur in an intramolecular process. The rearrangement of a 1-propargyl-1,2-dihydroisoquinoline into a 3-allenyl-3,4-dihydroisoquinolinium salt is also described.

IN PART VIII of this series[2] we summarised the literature concerning the intermolecular migration of a benzyl group from C_1 to C_3 of 1,2-dihydroisoquinoline derivatives, and we found that the two reactions, rearrangement and pavine formation, occur concurrently under all of the sets of conditions that we examined. It is interesting to note[3] that compounds of the type 1 undergo pavine-type cyclisation to 2 so readily that to achieve rearrangement to 3, an excess of acid has to be avoided. Knabe and Holtje[4] have found that



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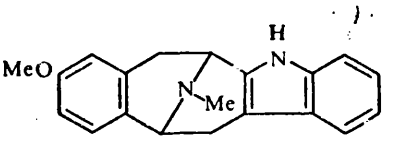

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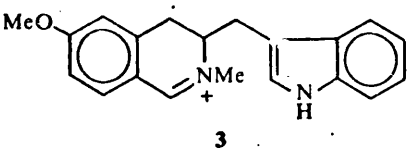
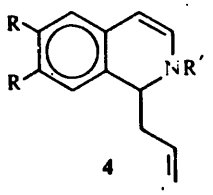


3

1-cinnimyl-1,2-dihydroisoquinolines will rearrange, but that, as expected, the 1-styryl derivatives undergo disproportionation without rearrangement.

We[2] have reported that 1-allyl-2-methyl-1,2-dihydroisoquinoline (4, R = H, R^1 = Me), formed by the addition of allyl magnesium bromide to isoquinoline methiodide, can be rearranged to the 3-allyl-3,4-dihydroisoquinolinium salt (5, R = H, R^1 = Me) in good yield. Knabe and Holtje[5] have also briefly described an allyl migration in 4 (R = OMe, R^1 = Me) to give high yields of 5 (R = OMe, R^1 = Me). In a discussion of the chemistry of benzylaminoacetaldehyde dimethyl acetals we[6] reported that when 6 (R = H) was treated with dilute HCl, it was transformed into the 3-allyl-3,4-dihydroisoquinolinium salt (5, R = OMe, R^1 = H) in almost quantitative



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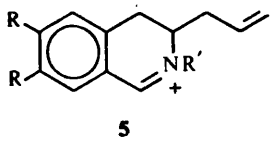
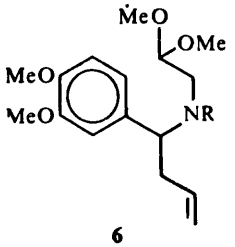


5

yield. Since we have now been able to isolate the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (7, R = OH, R^1 = H), and since compounds of this type are easily dehydrated by acids, it is clear that



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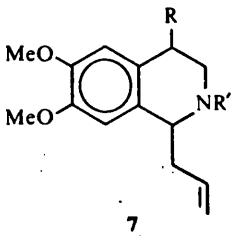

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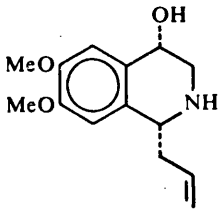
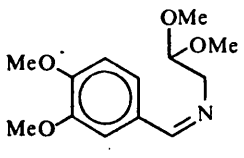


7a

the reaction proceeded via the 1,2-dihydroisoquinoline (4, R = OMe, R^1 = H). The NMR spectrum of 7 (R = OH, R^1 = H) can be interpreted in terms of a diastereomorphic mixture, the two components being present in nearly equal amounts. Crystallisation from acetone gave one pure isomer, and from the chemical shift positions of the C_5 and C_8 H atoms, it is concluded that it is the isomer shown as **7a**, on the basis of the reported[7] NMR data for the 1-methyl-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.

We[6] pointed out that the allyl migration reaction can be viewed as an example of a suprafacial sigmatropic [3,3] reaction, analogous to the Cope reaction, and as such may occur in a concerted manner under thermal conditions. In this paper we describe some experiments which show conclusively that the rearrangement of a 1-allyl-1,2-dihydroisoquinoline to the 3-allyl-3,4-dihydroisoquinolinium salt occurs by an intramolecular process. Some of this work has appeared in a preliminary form.[8, 9]

The substituted benzylaminoacetal (9, R = H) was prepared by the addition of crotyl magnesium bromide to the imine 8. Rearrangements of crotyl to methallyl



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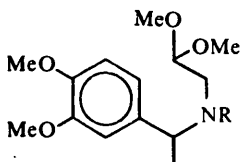
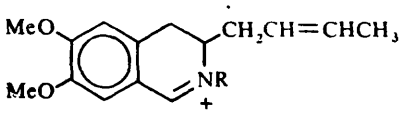


9

groupings in Grignard reactions are well known.[10, 11] The structure of 9 (R = H) follows from the NMR spectrum, which lacks absorption attributable to a $CH_3-\overset{|}{C}=C\overset{/}{\backslash}$ grouping. Two doublets in the region 0·72–1·06δ indicate that 9 (R = H) is a mixture of two diastereomorphs in the ratio of 2:1. The major component

was obtained pure by crystallisation of the mixture from acetone; its NMR spectrum exhibits a three proton doublet (J = 7·0 Hz) at 1·28δ and a three proton multiplet at 5·0–6·3δ. This pure diastereomorph, and the mixture of diastereomorphs were separately treated with dilute HCl when the same product was isolated in each case in yields of 96%. The NMR spectrum of this product indicates clearly that it is a 3-crotyl-3,4-dihydroisoquinoline (**10**, R = H), and we believe that the crotyl group has the *trans* geometry. Simultaneous irradiation of the methyl and methylene groups flanking the double bond permitted an estimate to be made of the coupling constant (15 Hz) between the olefinic protons, but the pattern in the olefinic region was not clearly defined. For an intramolecular rearrangement, the *cis*-crotyl product would also be expected, but it is possible that isomerisation to the more stable *trans* geometry occurs under the conditions of the reaction. Similar results were obtained when **9** (R = Me), prepared by reacting **9** (R = H) with methyl iodide, was treated with mineral acid. The product was shown to be **10** (R = Me) by the usual spectroscopic



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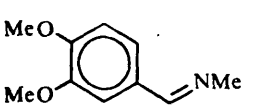
methods, but again some ambiguity concerning the geometry of the crotyl group remains. However, in both cases, the high yield of the 3-crotyl product with no detectable amounts of 3-methallyl-3,4-dihydroisoquinolinium salts, points strongly in favour of an intramolecular rearrangement.

A mixed migration experiment was next attempted, using equimolecular amounts of **6** (R = Me) and **9** (R = H). Only two products were formed, which were separated and shown to be identical with authentic samples of **5** (R = OMe, R^1 = Me) and **10** (R = H). The mass spectra of all four pure compounds (**5**, R = OMe, R^1 = H; **5**, R = OMe, R^1 = Me; **10**, R = H and **10**, R = Me), obtained by separately rearranging **6** (R = H; R = Me), **9** (R = H and R = Me), respectively, were compared with the spectra of the two products isolated from the mixed migration experiment. No evidence of crossed migrations was found. Considerable difficulty was experienced in preparing a sample of **6** (R = Me) free from the secondary amine **6** (R = H), and ultimately it was obtained from the Schiff base **11**. Addition of allyl magnesium bromide gave the expected secondary amine (**12**, R = $CH_2CH{=}CH_2$, R^1 = H) which was then alkylated with bromoacetal.



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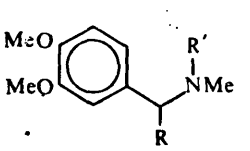

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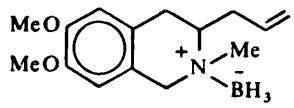
When **5** (R = OMe, R^1 = Me) was reduced with aqueous ethanolic $NaBH_4$ the product was the amine borane (**13**) and not the expected 1,2,3,4-tetrahydroisoquinoline (**14**). Although boranes of this type have been encountered before,[12] they were previously obtained with THF as the solvent.



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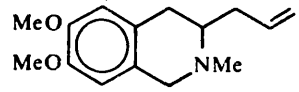
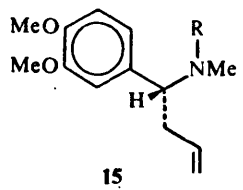


14

The required product (**14**) was obtained by hydrolysing **13** with 6N HCl.

Conclusive evidence for the intramolecular nature of the allyl migration reaction has now been provided by a study of the optically active benzylamine (**15**, R = H). The racemate (**12**, R = $CH_2CH{=}CH_2$, R^1 = H) was resolved with dibenzoyltartaric acid, and the isomer with $[\alpha]_D^{20}$ + 23·9° was found to have a very similar ORD curve (positive Cotton effect) to that[13] of *R*-α-phenyl-β-phenylethylamine of known absolute configuration. Treatment of **15** (R = H) with glycidol gave **15** (R = $CH_2CHOHCH_2OH$) which was converted to the aldehyde **15** (R = CH_2CHO) with



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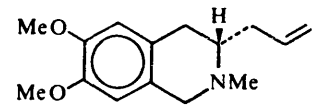
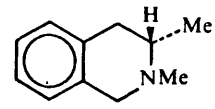


16

$NaIO_4$, and this, without isolation, was reacted with HCl under the conditions used previously. The product quaternary salt was reduced with $NaBH_4$, and the resulting tertiary base (**16**) had $[\alpha]_D^{20}$ + 35·0°. Resolution of a sample of **14**, obtained in the usual way from **6** (R = Me), with dibenzoyltartaric acid gave **16** with $[\alpha]_D^{20}$ + 36·9° so that the conversion of **15** (R = H) into **16** was accomplished with essentially 100% retention of optical activity. That the product possesses the *S*-configuration expressed in **16** was established by showing that the ORD curves of it and *S*-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17**) are very similar (plain positive). The required sample of **17** was prepared by the application of the Bischler–Napieralski reaction, followed by

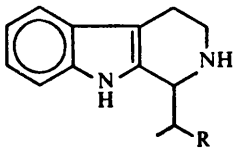


17

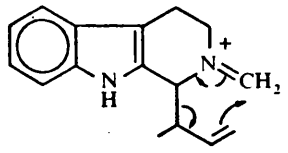
quaternisation and reduction, to (+)-amphetamine of known absolute configuration.

Thus, the sample of *R*-**15** (R = H) is converted in a stereospecific manner into a 3-allylisoquinoline derivative which has the *S*-configuration, as required[14] for an intramolecular rearrangement reaction.

It has been reported[15] that when **18** (R = $-CH{=}CH_2$) is treated with formaldehyde, the product is **20**; the reaction presumably involves **19** as an intermediate. We have now demonstrated an analogous reaction in the isoquinoline series; when **22** is reacted with formaldehyde in glacial acetic acid, an 82% yield of **23**, isolated as the pseudocyanide, is formed. The structure of the product follows from its mass and NMR spectral data. Winterfeldt and Franzischka[15] also described the rearrangement, under similar conditions, of **18** (R = $-C{\equiv}CH$) to the allene derivative **21**.



18



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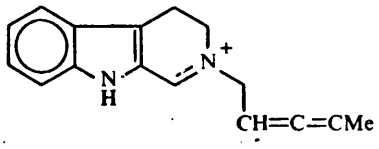

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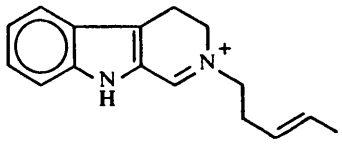

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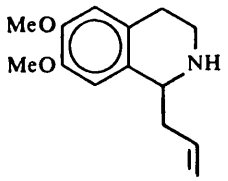

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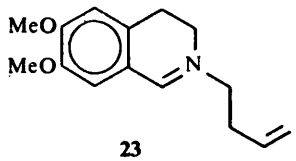
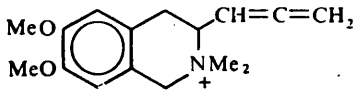


23

We have examined the reaction in which a 1-propargyl-1,2-dihydroisoquinoline was treated with mineral acid. Propargyl magnesium bromide was added to the imine (**11**) to yield the secondary amine (**12**, R = CH_2 C≡CH, R^1 = H), the structure of which follows from its mass spectrum and the characteristic NMR spectrum. Reaction of this acetylenic amine with glycidol yielded **12** (R = CH_2 C≡CH, R^1 = CH_2 CH(OH) CH_2 OH), which was oxidised with $NaIO_4$ to **12** (R = CH_2 C≡CH, R^1 = CH_2 CHO) and this aldehyde was treated with dilute HCl under the conditions used for the allyl migrations experiments. A 46% yield of a 3,4-dihydroisoquinolinium salt was isolated, but since it proved to be unstable it was characterised as **24** by reduction with $NaBH_4$ to the tertiary base and conversion to the methiodide. IR band



24

at 1970 cm^{-1} indicated the presence of an allene system in the molecule, and the NMR spectrum was found to be entirely compatible with structure **24**. Catalytic hydrogenation of the tertiary base formed by reduction of the rearrangement product with $NaBH_4$, yielded 2-methyl-3-n-propyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, identical with an authentic sample prepared by catalytic hydrogenation of **14**. The formation of a 3-allenyl-3,4-dihydroisoquinoline from a 1-propargyl-1,2-dihydroisoquinoline suggests that an intramolecular process operates in this rearrangement also.

EXPERIMENTAL

All m.ps are uncorrected, UV spectra were recorded in 95% EtOH soln and IR spectra were measured as nujol mulls. NMR spectra were recorded using a Varian A-60 spectrometer and chemical shifts are

measured in ppm, downfield from TMS as internal standard. GLC analyses were carried out using a Pye 104 gas chromatograph.

1-Allyl-6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (7; R = OH, R' = H). N-[4-(3,4-dimethoxyphenyl)butenyl] aminoacetaldehyde dimethylacetal hydrochloride (3·3 g) was dissolved in a mixture of conc HCl (25 ml) and crushed ice (25 g). After standing at RT overnight, the colourless soln was cooled to 0° and basified with 2N NaOH. The base was extracted with $CHCl_3$, dried and evaporated to give a gum, which, on trituration with acetone, gave 7 (R = OH, R' = H) as colourless prisms (1·55 g; 61%) m.p. 118–120°; ν_{max} cm^{-1}, 3330, 3120, 1645; NMR ($CDCl_3$) ppm, 6·98 s [0·4] (C_5—H of minor diastereomer). 6·91 s [0·6] (C_5—H of major diastereomer). 6·73 [0·6] (C_8—H. major isomer) 6·60 s [0·4] (C_8—H. minor isomer), 6·2–4·9 c [3] (—CH=CH_2), 4·45 m [1] (—CH(OH)), 3·9 s [6] (2 × —OCH_3), 3·9 m [1] (Ar—CH—N<), 3·3–2·3 c [4] (CH_2—CH=CH_2 and —CH(OH)—CH_2—N<), 2·85 s [2] (>NH and —CH OH; removed by deuteration).

Recrystallization from acetone yielded only one diastereoisomorph (**7a**; 0·5 g) m.p. 124–125°; NMR ($CDCl_3$) ppm, 6·88 s [1] (C_5—H), 6·73 s [1] (C_8—H). (Found: C, 67·6; H, 7·8; N, 5·6. $C_{14}H_{19}NO_3$ requires: C, 67·5; H, 7·7; N, 5·6%).

Acid treatment of **7a**. The base (249 mg, 0·001 mol) was dissolved in 6N HCl (15 ml) and heated at 100° for 1 hr. On cooling, the soln was diluted with water (20 ml) and basified with NH_4OH aq. Extraction with ether gave, after removal of solvent, a lemon oil (220 mg) 95%, the IR, UV and NMR spectra of which were identical with 3-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline.

N-[4-(3,4-Dimethoxyphenyl)-3-methyl-butenyl]aminoacetaldehyde dimethyl acetal (**9**, R = H). N-[3,4-Dimethoxybenzylidene)aminoacetaldehyde dimethyl acetal (31·4 g) was dissolved in dry ether (50 ml) and crotyl magnesium bromide (0·2 mol) in ether (250 ml) was added slowly. After stirring for 0·5 hr at RT, the reaction mixture was heated under reflux for 1 hr and then cooled. Finally 20% NH_4Cl aq (250 ml) was added, to destroy the excess reagent, and the aqueous phase was separated and extracted with ether. The combined ether phase and extracts were re-extracted with ice cold 2N H_2SO_4 (1 × 200 ml, 3 × 50 ml). The acid extracts were washed with ether, basified with NH_4OH aq and extracted with ether (3 × 100 ml). The combined extracts were dried and evaporated to yield a lemon oil (26·4 g, 69%), distillation of which gave a fraction, b.p. 158–163°/0·2 mm (21·4 g, 56%) of **9**, R = H). ν_{max} cm^{-1}, 3370, 3090, 1645, 915; NMR ($CDCl_3$) ppm, 6·9 s [1] and 6·8 s [2] (aromatic protons); 6·2–4·8 c [3] (—CH=CH_2); 4·4 t [1], J = 6 Hz (—CH_2—CH(OCH_3)$_2$); 3·9 s [3] and 3·85 s [3] (2 × Ar OCH_3); 3·6 c [1] (—CH—CH<); 3·32 s [3] and 3·30 s [3] (2 × —CH(OCH_3)$_2$); 2·6 d [2], J = 6 Hz (—CH_2—CH(OCH_3)$_2$); 2·4 c [1] (Ar—CH—CH<); 1·8 broad s [1], removed with D_2O, (>NH); 1·0 d [2], J = 7 Hz (>CH—CH_3), major diastereomer; 0·8 d [1], J = 7 Hz (>CH—CH_3, minor diastereomer). (Found: C, 66·3; H, 8·7; N, 4·9. $C_{17}H_{27}NO_4$ requires: C, 66·0; H, 8·8; N, 4·5%).

Monomethylation of this product with MeI (molar equiv) in acetone at RT over Na_2CO_3 gave **9** (R = CH_3) in 90% yield.

Treatment of a solution of **9** (R = H) in ether with HCl (g) gave a lemon solid, m.p. 128–130°; NMR ($CDCl_3$) ppm, 1·35 d [2], J = 7 Hz (>CH—CH_3, major isomer); 1·05 d [1], J = 7 Hz (>CH—CH_3, minor isomer). Two recrystallizations from acetone yielded a sample of the hydrochloride of the major diastereomorph (**9**, R = H) as colourless needles m.p. 134–135°. NMR ($CDCl_3$) ppm, 1·3 d [3], J = 7 Hz (>CH—CH_3).

Acid treatment of **9** (R = H). The mixed diastereomorphs of the secondary base (3·0 g) were dissolved in EtOH and conc HCl (1:1; 50 ml) and heated at 100° for 3 hr. The mixture was diluted with water (200 ml) and washed with ether (3 × 50 ml): basification of the aqueous phase with NH_4OH, followed by ether extraction, gave, after removal of the dried solvent, a yellow oil (2·4 g, 98%) of **10a**. Al_2O_3 TLC (10% EtOH in $CHCl_3$) showed one spot R_f 0·55, GLC (5′ × ¼″ column of 5% SE 30 silicone rubber on 85–100 mesh Universal B) column temp 150°, N_2 flow rate 30 ml/min indicated one component retention time 2 min 40 sec; mol wt. (mass spec) 245; λ_{max} nm, 234, 285, 315—almost identical with UV spectrum of 6,7-dimethoxy-3,4-dihydroisoquinoline; ν_{max} cm^{-1}, 3030, 1630, 970; NMR ($CDCl_3$) ppm, 8·2 d [1], J = 3 Hz

(Ar—CH=N—); 6·8 s [1] and 6·65 s [1] aromatic protons); 5·9–5·2 c [2] (—CH—CH=CH—CH_3); 3·85 s [6] (2 × —OCH_3); 3·6–2·1 c [5] (aliphatic protons); 1·8–1·5 c [3] (—CH=CH—CH_3). Simultaneous irradiation of methyl and methylene protons flanking the double bond of the crotyl side chain reveals the olefinic coupling constant to be approx 15 Hz.

The hydrochloride was prepared and recrystallized from acetone as pale yellow crystals m.p. 188–189°; ν_{max} cm^{-1}, 3030, 2520, 1650, 970. λ_{max} (ε) nm, 211 (9300), 248 (15,700), 313 (8100), 370 (6000). (Found: C, 63·3; H, 7·4; N, 5·1; Cl, 12·6. $C_{15}H_{20}NO_2Cl$ requires: C, 63·9; H, 7·2; N, 5·0; Cl, 12·6%). The pure diastereomorph of the secondary base **9** (R = H) was similarly treated with acid, and the product was identical in all respects to that obtained by acid treatment of the mixed diastereoisomorphs.

The base **10a** (2·95 g) was dissolved in aqueous EtOH and treated with $NaBH_4$ (3 g) and allowed to stand overnight at RT. The soln was evaporated to half bulk and treated with H_2O (50 ml) and ether (50 ml). The ether layer was separated, dried ($MgSO_4$) and the hydrochloride ppt'd with HCl (g). This salt was recrystallized from EtOH as lemon coloured needles (2·0 g, 59%) m.p. 211–212°; λ_{max} (ε) nm, 232 (5600), 287 (2900); ν_{max} cm^{-1}, 3040, 2740, 2620, 2540, 2505, 2460, 970. (Found: C, 63·2; H, 7·6; N, 5·0. $C_{15}H_{22}NO_2Cl$ requires: C, 63·5; H, 7·8; N, 4·9%).

Acid treatment of **9** (R = CH_3). The tertiary base (3·23 g, 0·01 mol) was heated with 6N HCl (25 ml), at 100° for 3 hr. After cooling, dilution with water (100 ml) and basification to pH 8 with $NaHCO_3$, the soln was washed with ether (3 × 25 ml). [A small amount of **10a** was obtained from the ether layers, indicating the presence of **9** (R = H) in the tertiary base.] The aqueous soln was treated with NaCN (0·5 g) and again extracted with ether (4 × 25 ml), to give, after removal of solvent, a colourless waxy solid (2·65 g, 93%), which when triturated with ether had m.p. 70–71°; λ_{max} (ε) nm, 238 (7800), 288 (3600), 315 (2300), 373 (2300); ν_{max} cm^{-1}, 2800, 2015, 965; NMR ($CDCl_3$) ppm, 6·70 s [1] and 6·63 s [1] (aromatic protons) 5·84–5·26 m [2] (—CH_2—CH=CH—CH_3), 4·73 s [1] (Ar—CH—CN), 3·8 s [6] (2 × —OCH_3), 3·3–2·3 m [5] (Ar—CH_2—CH—CH_2—) 2·6 s [3] (>N—CH_3), 1·7 c [3] (—CH=CH—CH_3). (Found: C, 70·8; H, 7·5; N, 10·0. $C_{17}H_{22}N_2O_2$ requires: C, 71·3; H, 7·7; N, 9·8%).

N-[4-(3,4-Dimethoxyphenyl) butenyl] methylamine (**12**, R = —CH_2CH=CH_2, R^1 = H). Procedure as for **9**, R = H), but using compound **11** (35·8 g, 0·2 mol) and allyl magnesium bromide (0·25 mol). After removal of ether solvent, a pale yellow oil was obtained (35·8 g), which was purified via the hydrochloride. The latter recrystallized from EtOH as colourless plates, m.p. 167–168°; ν_{max} cm^{-1}, 2800, 2710, 2440, 1645. (Found: C, 61·2; H, 7·8; N, 5·7. $C_{13}H_{20}NO_2Cl$ requires: C, 60·6; H, 7·8; N, 5·4%). The pure base was obtained from the hydrochloride as a colourless oil, λ_{max} (ε) nm, 231 (8200), 281 (2800); ν_{max} cm^{-1}, 3330, 2790, 1640; NMR ($CDCl_3$) ppm, 6·9 s [1] and 6·8 s [2] (aromatic protons); 6·1–4·8 c [3] (—CH_2—CH = CH_2), 3·82 s [3] and 3·78 s [3] (2 × OCH_3); 3·45 m [1] (Ar—CH—N<), 2·4 m [2] (>CH—CH_2—CH = CH_2); 2·2 s [3] (>N—CH_3), 1·4 broad s, removed by D_2O (>NH).

N-[4-(3,4-Dimethoxyphenyl butenyl]-N-methyl aminoacetaldehyde dimethyl acetal (**6**, R = CH_3). Bromacetal (5·72 g, 0·034 mol) and **12** (R = —CH_2—CH=CH_2, R^1 = H; 8·4 g, 0·034 mol) were heated at 120° for 2 hr with rapid stirring. The cooled mixture was dissolved in water (100 ml) and ether (50 ml); the aqueous layer was separated and extracted with ether (2 × 50 ml). The combined ether phase and extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil (10·2 g, 87%) which was distilled under reduced pressure to give **6** (R = Me) as an oil (7·3 g, 61%), bp 130–133°/0·3 mm. This material was basically identical with previous sample of **6** (R = CH_3), but was free from **6** (R = H).

Attempted crossed migration experiment (**6**, R = CH_3; 1·00 g) and **9** (R = H; 1·00 g) were dissolved in 6N HCl (15 ml) and heated at 100° for 1 hr. On cooling, the soln was diluted with water (50 ml) and washed with Et_2O (3 × 10 ml). The soln was then basified with $NaHCO_3$ to pH 8 and extracted with ether (5 × 10 ml); after drying the combined extracts were evaporated to give a colourless oil (A) (0·75 g). The aqueous phase was treated with NaCN (0·5 g), extracted with ether (5 × 10 ml) and these extracts evaporated to give a lemon coloured waxy solid (B) (0·86 g).

The base A was shown to be identical with **10a** previously obtained (IR, NMR and mass spectra), rigorous TLC and GLC analysis did not detect that cross migration had occurred, whereas a synthetic mixture of **5a** (R = —OCH_3; 5%) and **10a** (95%) was easily analysed (GLC as before, retention times 1 min 55 sec and 2 min 40 sec respectively).

The pseudo cyanide (B) was similarly shown to be identical to the pseudo cyanide of **5** (R = OCH_3, R' = CH_3), this too was a single compound. GLC showed a single peak under a variety of conditions. Using the same column packing and flow rates as previously described, but at 200°, a peak with a retention time of

2 min 15 sec, identical to that of a pure sample was obtained. A mixture of the pseudo cyanide of **10** (R = CH_3; 5%) and the pseudo cyanide of **5** (R = OCH_3, R' = CH_3; 95%) was easily analysed by GLC showing retention times of 3 min 0 sec and 2 min 15 sec respectively at 200°. The mass spectra of B showed no peaks above *m/e* 245.

Reduction of **5** (R = OCH_3; R' = CH_3) with $NaBH_4$. The salt (500 mg) in EtOH (10 ml) was treated with $NaBH_4$ (500 mg) at room temp. After 2 hr the soln was diluted with water (50 ml) and extracted with ether (3 × 25 ml). After removal of the ether, the residue (an oil + needle-like crystals) was crystallised from a small volume of EtOH to yield colourless needles (170 mg) of **13** m.p. 137–138°; ν cm^{-1} 2380, 2330, 2290, 1640; λ_{max} mn (ε): 226 (6000), 287 (3300). M.W. (mass spec) 261. (Found: C, 69·5; H, 9·6; N, 6·0. $C_{15}H_{24}BNO_2$ requires: C, 69·0; H, 9·3; N, 5·4%).

The boron complex **13**, combined with the mother liquors from its crystallisation, was treated with conc HCl on a steam bath for ½ hr. After dilution, basification and extraction with ether, a colourless oil (420 mg) was isolated which was shown (UV, NMR, IR) to be identical with **14**.[6]

Resolution of N-[4-(3,4-*dimethoxyphenyl*)-*butenyl*]-*methylamine* (**12**; R = $-CH_2-CH=CH_2$, R' = H). The base (10·0 g) was dissolved in acetone (100 ml) containing (−) dibenzoyl tartaric acid (32·4 g) warmed to about 60°, cooled and left at 0° overnight. The colourless crystalline product (10·4 g) which had separated was collected and recrystallised from acetone ether (1 : 1) a total of six times, until a constant optical rotation of $[\alpha]_{20}^{D} = -78°$ (2% in EtOH) was obtained. The purified salt (3·5 g) was basified with $NaHCO_3$ and the liberated base was extracted into ether. Removal of the solvent gave **12** (R = $-CH_2-CH=CH_2$, R' = H) as a colourless oil (0·8 g) $[\alpha]_{20}^{D} = +23·9$ (8% in EtOH), ORD (in isooctane) shows plain (+)ve curve, with (+)ve Cotton effect at 285 nm. Comparison with ORD curve of *R*-(α)-phenyl-β-phenylethylamine [(+)ve plain curve, (+)ve Cotton effect at 269 nm] indicates that this compound has the *R* configuration e.g. **15** (R = H).

Isolation of **16** *after rearrangement.* The base **15** (R = H) (700 mg) and glycidol (300 mg) were heated together at 100° for 2 hr. On cooling, water (10 ml) and $CHCl_3$ (10 ml) were added, and the temp reduced to 0°. $NaIO_4$ (610 mg) in water (10 ml) was added slowly, and the pH was adjusted to 8 with NaOH aq. After stirring at RT for 3 hr, the $CHCl_3$ layer was separated and the aqueous phase extracted with $CHCl_3$ (3 × 5 ml). The combined $CHCl_3$ phase and extracts were re-extracted with 6N HCl (4 × 5 ml) and the acid extracts were heated at 100° for 1 hr, cooled, and diluted with water (50 ml). The soln was basified with $NaHCO_3$ and washed with ether (2 × 25 ml), then treated with $NaBH_4$ (500 mg) at RT for 1 hr. The resultant mixture was acidified with 2N HCl and heated at 100° for a few min, then cooled, basified and extracted with ether (4 × 25 ml) to give the corresponding 1,2,3,4-tetrahydrobase as a colourless oil (273 mg) $[\alpha]_{20}^{D} = +31·1°$. The base was passed down a column of alumina, eluting with $CHCl_3$, and the product was then crystallized from light petroleum (40–60°) as colourless plates (210 mg) m.p. 44–45°, $[\alpha]_{20}^{D} = +35·0°$. (Found: C, 72·6; H, 8·5; N, 5·6. $C_{15}H_{21}NO_2$ requires: C, 72·8; H, 8·6; N, 5·7%), ORD (isooctane) show plain (+)ve curve. Comparison with ORD curve of *S*-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17**), which is very similar, supports the configuration **16**. The specific rotation of this product compared with that of **16** prepared by the resolution of **14** indicates that at least 97% retention of configuration is maintained during rearrangement.

Resolution of **14**. The 3-allyl tetrahydroisoquinoline (2·47 g) and (−)-dibenzoyl tartaric acid (1·79 g) were dissolved in acetone (10 ml) and cooled to −30°. After standing overnight the solid product which had formed was collected and recrystallised from acetone a total of eight times. After basification with ammonia soln the free base, from this salt, was extracted into ether and, after removal of the solvent, was obtained as a colourless solid. Recrystallisation from light petroleum (40–60°) gave plates (179 mg) m.p. 45–46° $[\alpha]_{20}^{D} = +36·9°$.

S-2,3-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**17**). (+)-*S*-Amphetamine (6·75 g) $[\alpha]_{D}^{20}$ +33·6° and formic acid (3·7 g) were heated together in an open flask for 3 hr at 180°. The resultant oil was dissolved in H_3PO_4 (s.g. 1·75; 30 ml) and P_2O_5 (50 g) added. The mixture was heated for 3 hr at 200–210° with occasional stirring. After cooling, the mixture was poured onto crushed ice (500 ml) and the aqueous soln was then washed with benzene (3 × 100 ml).

The aqueous soln was then basified with $NaHCO_3$ and extracted with benzene (3 × 100 ml); removal of the dried solvent affording a yellow oil, λ_{max} 257 nm ν_{max} cm^{-1}, 1630, which was dissolved in acetone (30 ml) and treated with MeI (5 ml). Yellow needles soon formed; these were collected and crystallised from acetone (6·92 g; 48%) m.p. 155–156°; NMR (CF_3CO_2H) ppm 9·1 broad s [1] ($C_1-\underline{H}$); 8·1–7·4 m [4] (aromatic protons); 4·4 m [1] ($-CH_2-\underset{|}{\overset{|}{CH}}-CH_3$); 4·0 s [3] ($\underset{\diagdown\ \diagup}{\overset{+}{N}}-CH_3$); 3·8–2·8 c [2] ($Ar-CH_2-\underset{|}{CH}-$); 1·45 d

This salt (4·62 g) was dissolved in EtOH (25 ml) and $NaBH_4$ (2·0 g) added slowly. Water was then added, and the reaction mixture extracted with ether; removal of the dried solvent afforded a colourless oil (2·05 g, 79%), purified as the hydrochloride: colourless needles, m.p. 216–217° (EtOH). (Found: C, 66·9; H, 8·1; N, 7·1. $C_{11}H_{16}NCl$ requires: C, 66·8; H, 8·2; N, 7·1%). The pure base, liberated from the hydrochloride salt, was a colourless liquid. λ_{max} (ε) nm, 267 (500), 274 (500), ν_{max} cm^{-1}, 2800, 1380; NMR ($CDCl_3$) ppm 7·1 s [4] (aromatic protons; 3·8 d [1], J = 15 Hz and 3·55 d [1], J = 15 Hz (Ar—CH_2—N<); 3·0–2·5 c [3] (Ar—CH_2—CH—N<); 2·4 s [3] (>N—CH_3); 1·15 d [3], J = 7 Hz (>CH—CH_3), $[\alpha]_{20}^{D}$ = +89·8° (10% in EtOH); ORD plain (+)ve curve with (+)ve Cotton effect at 278 nm.

Preparation of **23**. 1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (250 mg) in glacial AcOH (2·0 ml) and 40% HCHO soln (1·0 ml) was heated at 100° for 2 hr. After the addition of water (50 ml) and basification, the soln was washed with ether (3 × 10 ml). KCN (0·5 g) was then added and the cloudy suspension which formed was extracted with ether (3 × 10 ml). Removal of solvent from the combined dried extracts yielded a colourless solid (207 mg), which was recrystallised from benzene/petrol (40–60°). m.p. 78–79°; λ_{max} (ε) nm, 238 (6300), 288 (2800), 293 (2800), 316 (2200), 372 (2100); ν_{max} cm^{-1}, 2210, 1645; NMR ($CDCl_3$) ppm, 6·85 s [1] and 6·80 s [1] (aromatic protons), 6·2–4·9 c [3] (—CH_2—CH=CH_2). 4·8 s [1] (Ar—CH—CN), 3·9 s [6] (2 × —OCH_3), 3·2–2·2 c [8] (Ar—CH_2—CH_2—N—CH_2—CH_2—). (Found; C, 71·0; H. 7·4; N, 10·4. $C_{16}H_{20}N_2O_2$ requires: C, 70·6; H, 7·4; N, 10·3%).

N-methyl-1-(3,4-dimethoxy)phenylbut-3-ynamine (**12**, R = —CH_2—C≡CH, R′ = H). A soln of propargyl magnesium bromide (from 40 g propargyl bromide) in ether (240 ml) was added slowly to a soln of N-methylveratraldehyde imine (36 g) in ether (50 ml) at 0°. After stirring for 2 hr the reaction was heated at reflux for a further 30 min. The Grignard complex was then cautiously decomposed with 20% NH_4Cl aq, diluted with water (1 l) and the organic phase separated. After extraction with ether (5 × 50 ml) the combined ether layers were dried and evaporated to leave a brown oil (30 g), this was dissolved in benzene and the soln saturated with HCl. The solid which formed was collected and recrystallised from EtOH as colourless needles m.p. 222–224°; ν_{max} cm^{-1}, 3200, 2840, 2700–2200, 1610. (Found: C, 60·9; H, 7·1; N, 5·5. $C_{13}H_{18}NO_2Cl$ requires: C, 61·1; H, 7·1; N, 5·5%).

After basification with ammonia soln the corresponding base **12** (R = CH_2—C≡CH, R′ = H) was obtained as a pale brown oil (21 g) 46%, which solidified on standing, and was recrystallised from 60–80° light petroleum as colourless needles m.p. 71°. Mass *m/e* 219 (m+) [3%], 180 [100%]; ν_{max} cm^{-1}, 3600–3200, 2820, 2780, 2100; NMR ($CDCl_3$) ppm, 7·0–6·9 broad s [3] (aromatic protons), 3·9 s [6] (2 × —OCH_3), 3·7 t [1], J = 7 Hz (Ar—CH—CH_2—), 2·5, m [2] (—CH—CH_2—C≡CH), 2·3 s [3] (—N—CH_3), 2·0 t [1], J = 2·5 Hz (—CH_2—C≡CH), 1·9 s [1] (—NH) removed by deuteration.

Rearrangement of **12** (R = CH_2—C≡CH, R′ = H). The above compound (4·8 g) was heated with glycidol (1·5 g) at 100° for 2 hr. Chloroform (40 ml) and water (40 ml) were introduced, the mixture cooled to 0°, and sodium metaperiodate (5·0 g) in water (30 ml) was then slowly added. The reaction mixture was basified with NaOH (pH 8) and vigorously stirred for 3 hr. The chloroform layer was then separated and the aqueous phase extracted with chloroform, the chloroform layer and extracts were combined and re-extracted with 6N HCl (3 × 50 ml). The acid extracts were heated at 100° for 1 hr, cooled, diluted with water (250 ml), washed with ether (3 × 30 ml) and finally basified with $NaHCO_3$ aq. $NaBH_4$ (8 g) in small amounts was added to the aqueous soln and, after the reaction had ceased, the tertiary base formed was collected into ether. Removal of the ether afforded a brown oil (2·0 g) λ_{max} (ε) nm, 287 (1850); ν_{max} cm^{-1}, 1955, 1615, 1515; NMR ($CDCl_3$) ppm 6·6 s [1] and 6·55 s [1] (aromatic protons), 5·1 m [1] —CH=C=CH_2) 4·8–4·6 m [2] (—CH=C=CH_2), 3·85 s [6] (2 × OCH_3), 3·7 q [2], J = 2 Hz (Ar—CH_2—N<), 3·0–2·6 m [3] (Ar—CH_2—CH—), 2·45 s [3] (—NCH_3).

This material was characterised as **24**, colourless plates m.p. 212–213° (EtOH); mass *m/e* 260 (m+) [83·5%], 215 [78%], 206 [100%]; λ_{max} (ε) nm, 287 (2400), ν_{max} cm^{-1}, 1970, 1615, 1520; NMR (CF_3CO_2H) ppm 6·9 s [1] and 6·85 s [1] (aromatic protons), 5·6–5·0 m [3] (—CH=C=CH_2), 4·8–4·6 m [2] (Ar—CH_2—N^+—),

4·4–4·2m[1](Ar—CH_2—CH—), 3·95s[6](2 × OCH_3), 3·4s[3](—N^+—CH_3), 3·4–3·2m[2](Ar—CH_2—CH—) 3·1 s [3] (—N^+—CH_3). (Found: C, 49·7; H, 5·9; N, 3·4. $C_{16}H_{22}NO_2I$ requires: C, 49·7; H, 5·7; N, 3·6%).

6,7-Dimethoxy-2-methyl-3-n-propyl-1,2,3,4-tetrahydroisoquinoline. The tertiary base from the rearrangement product, formed in the previous experiment, was hydrogenated at 5 atm pressure in acetone soln using 5% Pd–C as catalyst. After 15 hr at room temp the 3-n-propyl-tetrahydroisoquinoline was obtained as a colourless oil. This material was identical in all respects with a specimen prepared by the hydrogenation of **14** under the same conditions. Further characterisation was achieved by direct comparison of methiodides of the two samples; the methiodide was obtained as a colourless crystalline solid m.p. 246–247°; mass *m/e* 264 (m+) [0·06%], 206 [100%], λ_{max} (ε) nm, 287 (2100); ν_{max} cm^{-1}, 2845, 1615, 1520; NMR (CF_3CO_2H) ppm, 6·95 s [1] and 6·9 s [1] (aromatic protons), 4·65 m [2] (Ar—CH_2—$^+$N—), 4·0 s [6] (2 × —OCH_3), 4·0–3·5 m [1] (Ar—CH_2—CH—), 3·4 s [3] (—N^+—CH_3), 3·15 s [3] (—N^+—CH_3), 3·5–2·8 m [2] (Ar—CH_2—CH—), 2·2–0·8 m [7] (—CH—CH_2—CH_2—CH_3). (Found: C, 49·2; H, 6·6; N, 3·4; I, 32·1 $C_{16}H_{26}NO_2I$ requires: C, 49·1; H, 6·6; N, 3·6; I, 32·5%).

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SOME DIELS-ALDER REACTIONS WITH 4-VINYLISOQUINOLINE DERIVATIVES

(Tetrahedron, 1970, 26, 5969)

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SOME DIELS–ALDER REACTIONS WITH 4-VINYL ISOQUINOLINE DERIVATIVES

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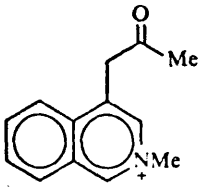
Abstract—The first preparation of 4-vinylisoquinoline derivatives is described. 1,4-Cycloadducts have been obtained by their interaction with the dienophiles maleic anhydride, acrylic acid, *p*-benzoquinone, propriolic acid and benzyne. The structures of the adducts have been assigned on the basis of chemical, but mainly spectroscopic evidence.

VERY few simple vinyl derivatives of isoquinolines have been prepared and studied. 1-Vinyl-3,4-dihydroisoquinoline has been obtained[1] from β-phenylethyl bromide and acrylonitrile, utilising an isoquinoline ring synthesis first reported by Lora–Tamayo *et al*[2] and 1-vinylisoquinoline itself has been prepared[3] by condensing 1-methylisoquinoline with formaldehyde and dimethylamine, followed by distillation over KOH. The formation of 1-styrylisoquinolines by condensation of 1-methylisoquinoline with aromatic aldehydes has been known[4] for some time, and 3-styrylisoquinolines can now[5] be prepared in a similar manner. 4-Styrylisoquinoline derivatives were first described by Abramovitch and Tertzakian[6] who utilised isoquinoline-4-acetic acid as starting material; more recently these compounds have been obtained[7] by applying the Wittig reaction to isoquinoline-4-aldehyde, and also by[8] condensing arylglyoxals with 1,2-dihydroisoquinolines, followed by reduction and dehydration. The last mentioned route is probably the most efficient one, although we[9] have also improved upon the original[6] method. Our interest in 4-substituted isoquinolines prompted us to synthesise 4-vinylisoquinoline derivatives in the belief that they might be useful intermediates in the synthesis of phenanthridines, benzo[*c*]phenanthridines and more complex heterocyclic compounds.

Our first approach was to condense 1,2-dihydroisoquinolines, generated either by reduction of isoquinolinium methosalts with LAH or by acid-catalysed cyclisation of benzylaminoacetals such as **3**, with suitable aldehydes. However, 2-methyl-1,2-dihydroisoquinoline failed to react with acrylaldehyde or propargylaldehyde, and the product **1** obtained[10] with pyruvic aldehyde could not be reduced and dehydrated to **2**.



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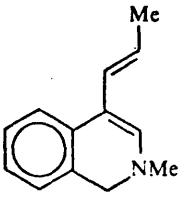

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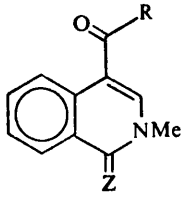
The Vilsmeir reaction,[11] which had been successfully used[12] to prepare indole-3-aldehyde, has now been applied to 2-methyl-1,2-dihydroisoquinoline, and yields of 33% of 4(R = H, Z = H_2) can be obtained. With 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline, the yield of the C_4-formyl derivative approaches 50%. As expected for a vinylogous amide, 4(R = H, Z = H_2) does not possess any carbonyl properties, but the derived isocarbostyril 4(R = H, Z = O), obtained from it by oxidation with MnO_2, condenses with 2,4-dinitrophenylhydrazine etc. With methyl magnesium bromide, 4 (R = H, Z = O) yields the expected alcohol **5**, which is easily oxidised with MnO_2 to 2-methyl-4-acetylisocarbostyril 4 (R = Me, Z = O). When



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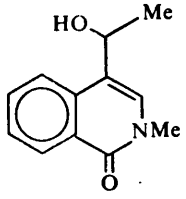

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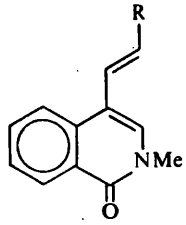

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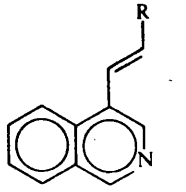

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4 (R = H, Z = O) was treated with methylene triphenylphosphorane only trace amounts of 6 (R = H) could be detected in the complex reaction mixture, but with carbomethoxymethylenetriphenylphosphorane, the diene ester 6 (R = CO_2Me) was formed. The same product was obtained more easily and in better yield by condensing 4 (R = H, Z = O) with malonic acid, followed by esterification. The structure 6 (R = CO_2Me) follows from the compound's mass spectrum and NMR spectrum All attempts to decarboxylate 6 (R = CO_2H) failed.

Isoquinoline-4-aldehyde, which is now[13] readily available, reacts with methylene triphenylphosphorane to give 4-vinylisoquinoline (45%), but although a unique NMR spectrum (Fig 1) was obtained on a freshly prepared sample, both it and the derived methiodide decomposed before elemental analysis could be carried out. The ester 7 (R = CO_2Et) is readily available from isoquinoline-4-aldehyde via the Wittig reaction.

There are very few reports in the literature concerning the use of isoquinoline derivatives as dienes in the Diels–Alder reaction.[14] Maleic anhydride reacts with isoquinoline itself,[15] and moderate yields of the expected adducts have been obtained with 1-styryl-6,7-dimethoxy-3,4-dihydroisoquinoline[16] and with 1-(1'-cyclohexenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline.[17]

When equimolecular amounts of 6 (R = CO_2Me) and maleic anhydride were heated under reflux in acetonitrile solution for 6 hr, a solid mp 245–246° separated slowly in

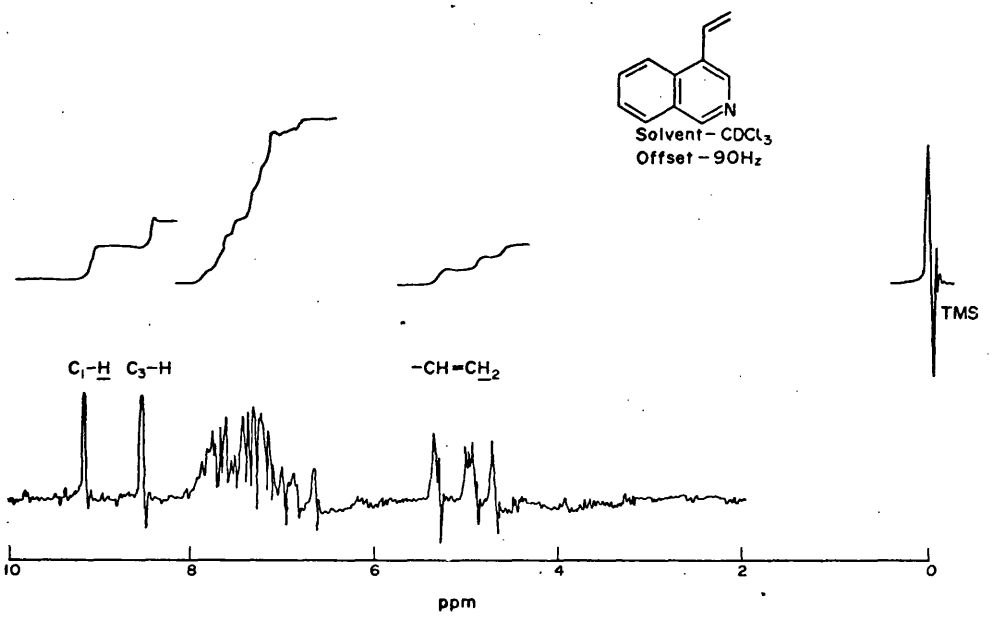
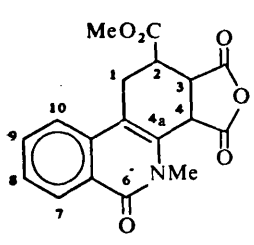


FIG. I

89% yield. This analysed correctly for the expected product (**8** or **9**; M.W. by mass spectrometry 341·088; $C_{18}H_{15}NO_6$ requires: 341·089). The UV spectrum of the adduct is similar to that of a styrene, but different from that expected for an isocarbostyril.



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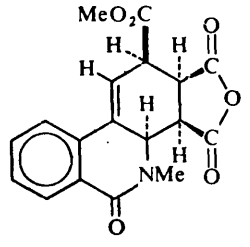

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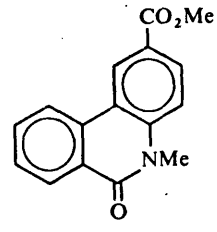

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The NMR spectrum at 60 MHz (in CF_3CO_2H soln) exhibited the required ratio of 2;1 for aliphatic:aromatic protons, thus supporting structure **9** rather than **8**. A complex one proton multiplet at 8·1 δ is assigned to the hydrogen at C_7; the only other recognisable absorptions were three proton singlets at 4·03 δ (OCH_3) and at 3·6 δ (NMe). In the IR spectrum, peaks at 1865 and 1770 cm^{-1} are associated with the absorptions due to a saturated anhydride, and a peak at 1750 cm^{-1} is assigned to the ester CO group. An amide CO band occurs at 1650 cm^{-1}. Conclusive evidence for the structure **9** (though not the stereochemistry indicated) is provided by an interpretation of the mass spectrum of the adduct, where the base peak (*m/e* 243) corresponds to the retro Diels–Alder reaction.[18] In fact the spectrum below *m/e* 243 is very similar to the spectrum of the diene ester **6** (R = CO_2Me) itself. The major fragmentations are interpreted as indicated in Chart I.

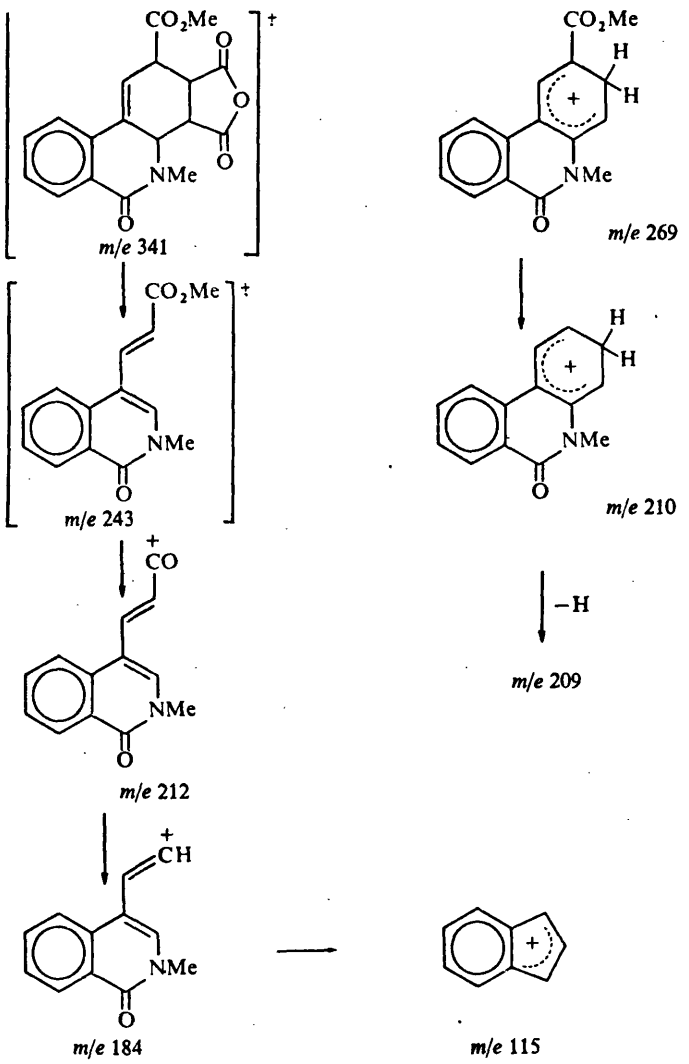


CHART I

From the known *trans*-geometry of the double bond αβ to the ester function in **6**(R = CO_2Me), and since the Diels–Alder reaction is a stereospecific *cis* addition leading to the endo adduct, the geometry implied in **9** is preferred for our product. This conclusion is strongly supported by a study of the NMR spectrum at 100 MHz (Fig 2). From the assignments made, and from the decoupling experiments, the following coupling constants have been estimated: $J_{1,2}$ = 4–5 Hz; $J_{1,4a}$ = 3 Hz; $J_{1,3}$ = 0 Hz and $J_{3,4}$ = 9 Hz. The value of $J_{1,2}$ suggests[19] that C_2-H is axial, and a value of $J_{1,4a}$ of about 3 Hz indicates an angle between C_{4a}-H and the perpendicular of about 25°, in agreement with that estimated from the Drieding model of **9**. The value for $J_{3,4}$ is in keeping with the dihedral angle of 20° observed on this model.

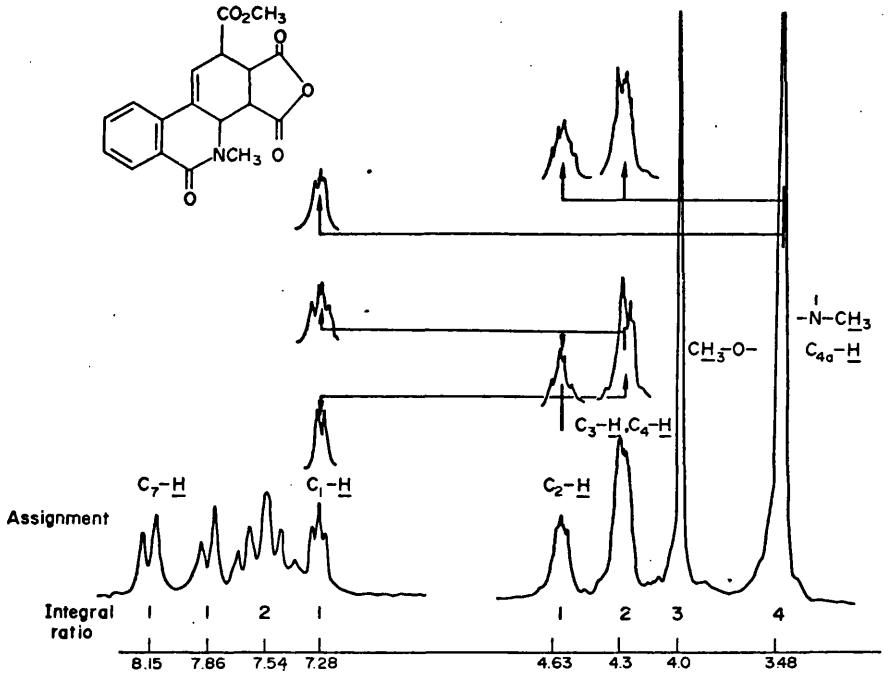
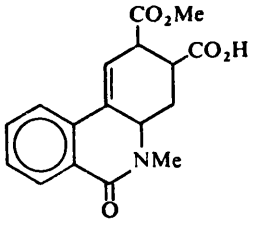


FIG. 2

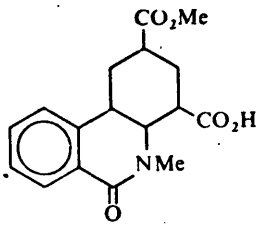
Since the C_{4a}-H signal is masked by the $\rangle NCH_3$ absorption, it is not possible to deduce the value of $J_{4,4a}$. However, simultaneous irradiation of C_1-H and C_{4a}-H leaves C_2-H as a poorly resolved quartet, and since this signal has a width of only 18–19 Hz, $J_{2,3}$ cannot be more than about 8–10 Hz, which corresponds to a dihedral angle between C_2-H and C_3-H of about 40°. The exo-adduct would have $J_{2,3}$ greater than 10 Hz, with a dihedral angle of about 180°.

The insolubility of the adduct **9** in the more common solvents frustrated most of the attempts to establish the structure by chemical methods. It has been reported[20] that alkaline potassium ferricyanide causes oxidative decarboxylation of dicarboxylic acids very similar in structure to our adduct, and when a solution of **9** in K_2CO_3aq was allowed to remain in contact with an excess of potassium ferricyanide for several days at room temperature, a 5% yield of the known[21] phenanthridone **10** was recovered.

With the successful addition of maleic anhydride to the diene ester **6** (R = CO_2Me), the reactions with other dienophiles were studied. With acrylic acid, an adduct was isolated in 85% yield, and of the two possible structures **11** and **12**, the expected isomer **11** is preferred from a study of the mass spectral fragmentation pattern (Chart II). As before, the base peak at *m/e* 243 is due to the retro Diels–Alder reaction leading to **6** (R = CO_2Me). However, a peak is observed at *m/e* 283 (M − 32) which is best interpreted as anhydride formation—a simple process for **11** but not for **12**. The ensuing fragmentations are then best explained on this basis. When the diene acid **6** (R = CO_2H) was condensed with acrylic acid, the resulting adduct was easily



11



12

transformed into an anhydride by reaction with acetic anhydride. Analogous adducts to **11** were formed when **6**(R = CO_2Me) was reacted with ethyl acrylate, acrolein and crotonic acid, although the purification problems were more severe. Curiously, acrylonitrile failed to react with **6** (R = CO_2Me).

When the diene ester **6** (R = CO_2Me) was reacted with an excess of *p*-benzoquinone, in boiling glacial acetic acid, a 60% yield of an adduct was isolated. The mass spectrum

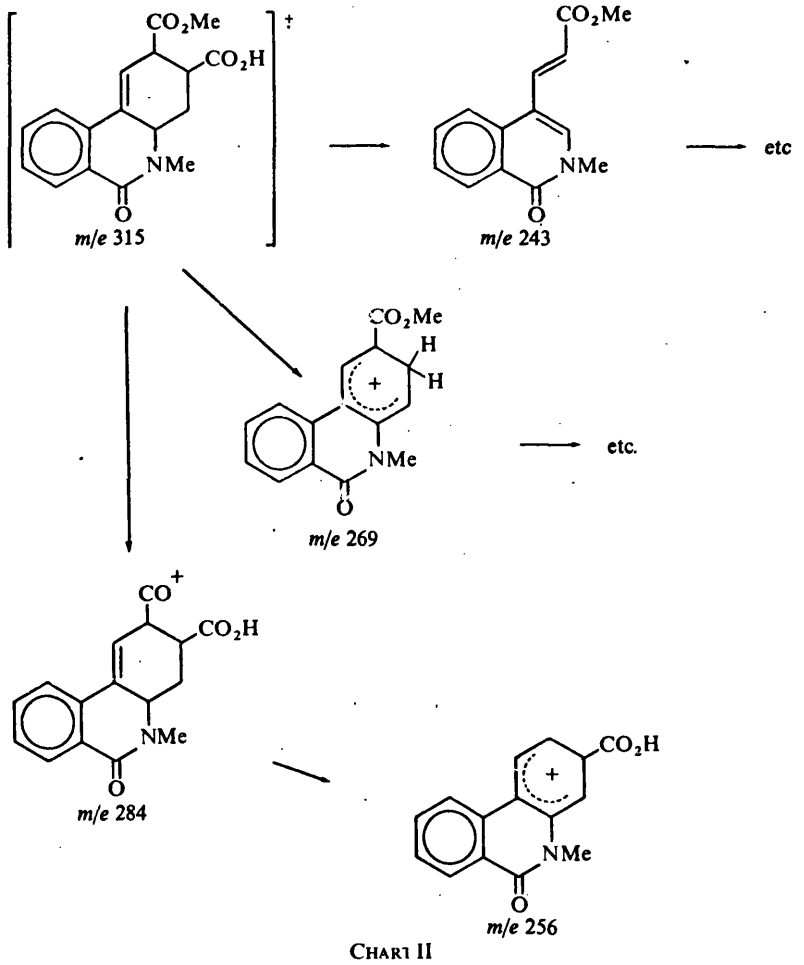
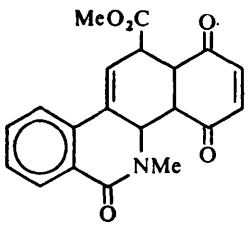
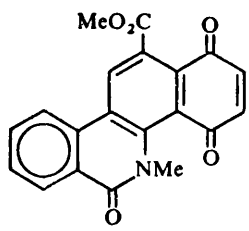


CHART II

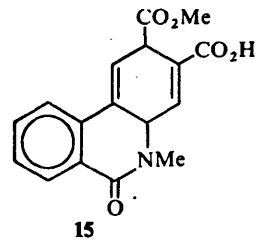




14

of this material indicated a molecular weight of 347, four units less than that required for the simple adduct **13**. That the adduct is **14** was concluded from an examination of the mass and NMR spectral data of the compound. The molecular ion is also the base peak in the mass spectrum, and significantly a retro Diels–Alder type of fragmentation does not occur in this case. The product **14** almost certainly arises via the expected adduct **13**, which is dehydrogenated by excess of *p*-benzoquinone (some quinhydrone was also isolated from the reaction mixture). This type of dehydrogenation reaction has been observed before[14] in diene reactions involving *p*-benzoquinone. The formation of **14** represents another[9a] synthesis of the benzo[*c*]phenanthridine ring system.

No reaction occurred between **6** (R = CO_2Me) and propriolic acid in boiling acetonitrile or in acetic acid, but in boiling xylene a product, $C_{17}H_{15}NO_5$ is formed and was isolated in 30% yield. It is not, however, the expected adduct **15**; the IR spectrum, for example, exhibits a sharp band at 3100 cm^{-1}, suggestive of a —CONH— group. The NMR spectrum exhibits absorptions due to SEVEN protons in the aromatic region (7·0–8·6 δ) and a three proton singlet at 3·9 δ (CO_2Me). The significant feature of the NMR spectrum is a three proton doublet (J = 7 Hz) at 2·6 δ, which



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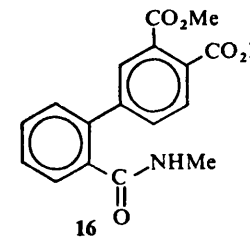
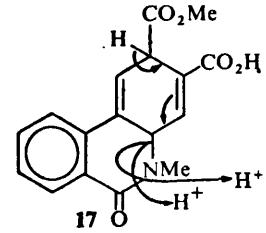


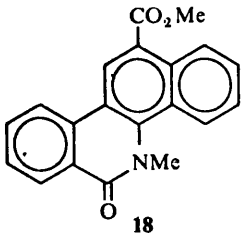
16

collapses to a singlet on deuteration. The structure **16** is proposed for this compound, and this is supported by the mass spectral data, where again no retro Diels–Alder fragmentation is observed. The formation of **16** is best rationalised by assuming that **15** is first formed, and that aromatisation occurs as indicated in **17**. Similar aromatisations have been observed[22] from Diels–Alder adducts involving enamines or dienamines.

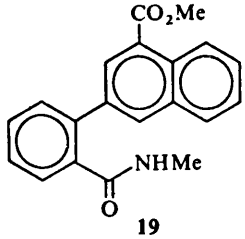


17 —— 16

An interest in aryne chemistry in this laboratory[23] prompted us to examine the reaction between diazotised anthranilic acid and the diene ester **6** (R = CO_2Me). After column chromatography over alumina, two crystalline solids were isolated in yields of 1·2% and 0·1%. These compounds were shown, by the usual spectroscopic methods, to be the benzo[*c*]phenanthridine **18** and the secondary amide **19**,



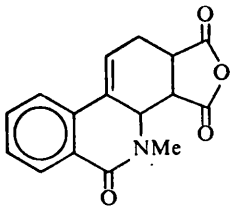
18



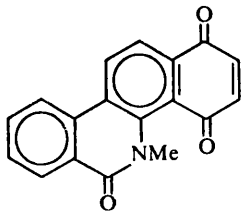
19

respectively, so that this reaction with benzyne shows the characteristics of both the *p*-benzoquinone and the propriolic acid pathways.

Our attempts to dehydrate **5** to **6** (R = H) failed, but when **5** was heated under reflux with maleic anhydride in acetonitrile solution, a 55% yield of the adduct **20**



20



21

was obtained. This technique has been used before[24] in Diels–Alder reactions. Repetition of the reaction with *p*-benzoquinone in place of maleic anhydride resulted in the isolation of **21** in 67% yield. Its structure follows from mass and NMR spectral data.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined on EtOH solns and IR spectra as nujol mulls. NMR spectra were measured with a Varian A60 spectrometer and chemical shifts are expressed as ppm downfield from TMS as internal standard.

2-Methyl-4-formyl-1,2-dihydroisoquinoline (**4**. R = H, Z = H_2)

2-Methyl-1,2-dihydroisoquinoline (from 20·0 g isoquinoline methiodide) in ether (200 ml) was added at 0° to the complex formed from $POCl_3$ (9·0 ml) and DMF. The resulting slurry was warmed at 50° for 2 hr, with removal of the ether. After cooling, crushed ice (150 g) and water (160 ml) were cautiously added, followed by a soln of NaOH (80 g) in water (160 ml). The yellow oil which slowly solidified, was crystallised from water containing a small amount EtOH to give off-white plates of **4** (R = H, Z = 2H), (14·3 g; 39%) m.p. 130–131°; λ_{max} nm (ε): 274(41,000), 335(35,3000); ν_{max} cm^{-1}: 1610, 1600; NMR ($CDCl_3$): 8·4 s [1] (—C<u>H</u>O); 8·1 m [1] (C_8<u>H</u>); 6·6 m [4] (3 adj. aromatic <u>H</u> + C_3<u>H</u>); 4·25 s [2] (Ar$C\underline{H}_2$N—); 2·8 s [3] ($\rangle NC\underline{H}_3$. [Found: C, 75·95; H, 6·4; N, 8·1, $C_{11}H_{11}NO$ requires: C, 76·4; H, 6·4, N, 8·1%].

2-Methyl-4-formyl-6,7-dimethoxy-1,2-dihydroisoquinoline

This was obtained in 47% yield from 2-methyl-6,7-dimethoxyisoquinolinium iodide by the above method. The required product had m.p. 134–135° (water); NMR ($CDCl_3$): 9·0 s [1] (—C<u>H</u>O); 8·39 s [1] (C_3<u>H</u>); 6·73 s [1] and 6·45 s [1] C_5<u>H</u> and C_8<u>H</u>); 4·51 s [2] (—C<u>H</u>$_2$); 3·94 s [3] and 3·72 s [3] (2 × —OC<u>H</u>$_3$); 2·94 s [3] (—NC<u>H</u>$_3$). [Found: C, 66·7; H, 6·3; N, 6·2. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%].

2-Methylisocarbostyril-4-aldehyde (4, R = H, Z = O)

A mixture of 4 (R = H, Z = O; 1·0 g), active MnO_2 (5·0 g) and acetone (100 ml) was stirred at room temp for 2 days. Removal of the MnO_2 and acetone, left a pale yellow solid, which was crystallised from water to give 2-methylisocarbostyril-4-aldehyde (0·95 g; 90%) m.p. 151–152°; λ_{max} nm (ε): 221(37,3000); 252(sh), 297 (9,950); ν_{max} cm^{-1}: 2730 (doublet); 1660, 1625, 1610; NMR (CF_3CO_2H): 9·8 s [1] (—C<u>H</u>O); 9·0 m [1] (—C_5<u>H</u>); 8·4 m [1] (C_8<u>H</u>); 8·13 s [1] (C_3<u>H</u>); 7·8 m [2] (C_6<u>H</u> + C_7<u>H</u>); 3·87 s [3] (—NC<u>H</u>$_3$). [Found: C, 70·9; H, 4·7; N, 7·4 $C_{11}H_9NO_2$ requires: C, 70·6; H, 4·8; N, 7·5%].

2-Methyl-4(α-hydroxyethyl)isocarbostyril (5)

MeMgI (from 0·5 g Mg and 1·5 ml MeI) in ether (100 ml) was added to a soln of 4 (R = H, Z = O; 1·0 g) in THF (50 ml). After stirring at room temp for 2 hr, the complex was decomposed with NH_4Cl soln. Water was added and the mixture was extracted with benzene. The organic layer was washed, dried ($MgSO_4$) and evaporated to leave a grey solid which was crystallised from petrol (80–100°): acetone (9:1). The product 5 (0·63 g; 60%) had m.p. 150–151°; λ_{max} nm (ε) 211(40,500); 292(10,250); 335(5,275); ν_{max} cm^{-1}: 3270, 1655, 1635, 1605; NMR ($CDCl_3$): 8·3 m [1] (C_8<u>H</u>); 7·7 m [3] (aromatic protons); 6·9 s [1] (C_3<u>H</u>); 4·0 s [1] (O<u>H</u>, removed by D_2O soln); 3·1 s [3] (—NC<u>H</u>$_3$); 5·15 q [1] (—C<u>H</u> — CH_3; J = 6·7Hz); 1·55 d [3] (C<u>H</u>$_3$CH—; J = 6·7 Hz). [Found: C, 70·2; H, 6·4; N, 6·8 $C_{12}H_{13}NO_2$ requires: C, 70·9; H, 6·45; N, 6·9%].

Simultaneous dehydration and addition reactions of 5

(a) *With maleic anhydride.* A mixture of 2-Methyl-4-(α-hydroxyethyl)-isocarbostyril (0·5 g) and maleic anhydride (0·5 g) was heated under reflux in acetonitrile soln (20 ml) for 17 hr. On cooling and standing, a colourless crystalline solid separated. This was collected and recrystallised from acetonitrile to give **20**; 55% yield m.p. 282–284; λ_{max} (ε) nm 224(42,150): 246(40,100); ν_{max} cm^{-1}: 1840, 1780 (—CO—O—OC—), 1650 (—CON<), 1610 (>C = C<); NMR (CF_3CO_2H). 7·5 m [1] (C_7<u>H</u>), 7·0 m [3] (aromatic protons), 6·3 m [1] (C_1—<u>H</u>); 4·1 – 1·0 m [5] (aliphatic protons) 2·9 s [3] (N— C<u>H</u>$_3$). [Found: C, 67·5; H, 4·8: N, 4·9 $C_{16}H_{13}NO_4$ requires: C, 67·8; H, 4·6: N, 5·0%]; mass (*m/e* 283 (10%), 185 (100%), 115 (12%).

(b) *With p-benzoquinone.* A mixture of 5 (0·5 g) and *p*-benzoquinone (0·5 g) was heated in boiling glacial AcOH (20 ml) for 6 hr. On cooling the soln was filtered and evaporated to leave a dark oil. On trituration with ether this crystallised and the dark brown product was then purified by chromatography on silica, eluting with chloroform. Recrystallisation from a large volume of 60–80° petrol gave off-white prisms of 21, mp > 320°, yield 0·47 g (67%); ν_{max} cm^{-1}, ~1660 (>CO), NMR ($CDCl_3$): 9·0–7·2 m [6] (aromatic protons), 7·0 s [2] (<u>H</u>C=C<u>H</u>), 3·5 s [3] (>N—C<u>H</u>$_3$). [Found: C, 74·5; H, 3·6; N, 4·6 $C_{18}H_{11}NO_3$ requires: C, 74·7; H, 3·8; N, 4·8%]; mass (*m/e*) 289 (100%), 272 (25%), 260 (80%), 232 (20%).

β-[4-(2-*Methylisocarbostyryl*)]*acrylic acid* (6, R = CO_2H)

A soln of 2-methylisocarbostyril-4-aldehyde (1·0 g), malonic acid (1·0 g) and piperidine (2 ml) in pyridine (20 ml) was heated under reflux for 3 hr. After cooling, the soln was carefully acidified (2N H_2SO_4) and the resulting ppt collected and washed (0·95 g; 80%). The product 6 (R = CO_2H) was purified by precipitation from Na_2CO_3 aq, m.p. 260° (dec); λ_{max} nm (ε): 221 (36,200), 330 (19.725); ν_{max} cm^{-1}: 3200–2500 (broad), 1690, 1660, 1610, 975; NMR (CD_3SOCD_3): 8·7–7·3 m [6] (4 aromatic protons + C_3<u>H</u> + 1 olefinic proton); 6.36 d [2] J = 16 Hz (—C<u>H</u>=C—), 3·53 s [3] (—NC<u>H</u>$_3$). [Found: C, 68·2; H, 5·0; N, 6·2. $C_{13}H_{11}NO_3$ requires C, 68·2; H, 4·8; N, 6·1%].

β-Methyl-[4-(2-methylisocarbostyril)]acrylate (**6**, R = CO_2Me)

The acid **6** (R = CO_2H) was reacted with MeOH and HCl to give **6** (R = CO_2Me) in 95% yield as a crystalline solid, m.p. 75–76° (MeOH-water); NMR ($CDCl_3$) 9·3–7·9 m [5] (C_3—H and aromatic protons, isoquinoline nucleus), 8·0 d [1] J = 16 Hz and 6·3 d [1] J = 16 Hz (—CH=CH—), 3·6 s [3] (—CO_2Me) and 3·35 s [3] (—NCH$_3$). [Found: C, 69·0; H, 5·3; N, 5·7 $C_{14}H_{13}NO_3$ requires: C, 69·1; H, 5·4; N, 5·8%]; mass (*m/e*) 243 (100%), 212 (55%), 184 (45%).

The ethyl ester was similarly prepared, colourless needles m.p. 89–90° (EtOH-water).

Diels–Alder reactions with the diene ester (**6**, R. = CO_2Me)

(a) *With maleic anhydride.* The ester (0·5 g) and maleic anhydride (0·5 g) were heated under reflux in acetonitrile soln (20 ml) for 6 hr. On cooling the white solid (**9**) which separated was removed and recrystallised from acetonitrile, yield 0·58 g (89%), m.p. 245–246°; λ_{max} 250, 335 nm. [Found: C, 63·8; H, 4·4; N, 4·6 $C_{18}H_{15}NO_6$ requires: C, 63·3; H, 4·4; N, 4·1%].

(b) *With acrylic acid.* A repetition of the above reaction using acrylic acid (5 ml) instead of maleic anhydride yielded an oil, after removal of the solvent. Trituration of this oil with ether afforded a colourless solid (**11**), which was recrystalised from dil AcOH, yield 0·49 g (85%), m.p. 222–224°; ν_{max} cm^{-1}, 3100–2500 (—OH), 1740 (>C=O), 1635 (>C=O). NMR (CD_3SOCD_3): 8·2–7·0 m [4] (aromatic protons), 6·5 m [1] (olefinic proton), 4·65–2·0 m [6] (aliphatic protons), 3·66 s [3] (—OCH$_3$), 3·0 s [3] (—NCH$_3$). [Found: C, 64·9; H, 5·3; N, 4·4 $C_{17}H_{17}NO_5$ requires C, 64·8; H, 5·4; N, 4·4%.]

(c) *With p-benzoquinone.* The ester (0·2 g) was heated with *p*-benzoquinone (0·5 g) under reflux in glacial AcOH (50 ml). for 4 hr. After removal of the solvent, the residue was heated at 150°/3 mm to remove impurities. Chromatographic purification on silica, eluting with CH_2Cl_2/EtOH (98:2), yielded colourless prisms (**14**), m.p. 262–263° (0·18 g, 75%) NMR ($CDCl_3$) 9·0–7·5 m [5] (aromatic protons); 7·3 s [2] (—CH=CH—), 3·7 s [3] (—CO_2CH$_3$), 3·0 s [3] (—NCH$_3$), mass (*m/e*) 347 [M^+] (100%), 330 (10%), 318 (10%), 289 (19%), 260 (18%). [Found: C, 69·8; H, 3·9: N. 4·3. $C_{20}H_{13}NO_5$ requires: C, 69·2; H, 3·8; N, 4·0%].

(d) *With propriolic acid.* The ester (0·5 g) was heated with propriolic acid (1 g) in xylene (50 ml) at reflux for 18 hr. On cooling a colourless ppt formed. This was removed and recrystallised from xylene to yield prisms (**16**), m.p. 229–231°, yield 0·32 g, 60%; ν_{max}cm^{-1}, 3400–2500 (—OH), 3100 (—NH), 1735 (—CO_2Me), 1700 (—CO_2H), 1620 (Ar CONHMe); mass (*m/e* 313 [M^+] (60%), 283 (50%), 265 (54%), 251 (100%), 238 (20%), 224 (22%), 207 (25%). M^+ = 313·0950 $C_{17}H_{15}NO_5$ requires: 313·095. [Found: C, 64·7; H, 4·8; N, 4·2 $C_{17}H_{15}NO_5$ requires: C, 65·2; H, 4·8; N, 4·5%).

(c) *With benzyne.* Solns of amyl nitrite (10ml) in acetonitrile (100 ml) and anthranilic acid (1·8 g) in acetonitrile (100 ml) were added concurrently to the diene ester (3 g) in acetonitrile (100 ml) at reflux during a 4 hr period. After a further 1 hr, the solvent was removed to give a dark oily product, which was dissolved in ether (50 ml). Acidic impurities were removed by washing with 2N NaOH and the ether was then evaporated to yield an oil (2·1 g). This material was chromatographed upon basic grade alumina (200 g).

Eluting Solvent	benzene (1,950 ml)	fraction A (0·01 g)
Eluting Solvent	25% $CHCl_3$ in benzene (1,520 ml)	fraction B (0·03 g)
Eluting Solvent	45% $CHCl_3$ in benzene (900 ml)	fraction C (1·10 g)
Eluting Solvent	75% $CHCl_3$ in benzene (1,800 ml)	fraction D (0·15 g)
Eluting Solvent	chloroform (1,370 ml)	fraction E (0·02 g)

Fractions A, B, D and E were shown by TLC to be complex mixtures, whereas fraction C contained two main components: this fraction on trituration with acetone afforded colourless prisms of **18**, which were recrystallised from acetone (0·5 g), m.p. 184–185°; λ_{max} (ε) nm 225 (21,400), 252 (28,400), 281 (49,900), 320 (12,400), 338 (12,400), 353 (10,100); ν_{max}cm^{-1} 1720 (—CO_2CH_3), 1670 (Ar CON<); NMR ($CDCl_3$): 8·6 s [1] 9(C_1—H), 9·0–8·1 m [8] (aromatic protons), 3·1 s [3] (—CO_2CH$_3$), 2·8 s [3] (—NCH$_3$); mass (*m/e*) 317 [M^+] (100%), 316 [M-1$^+$] (70%), 288 [M-31$^+$] (16%), 212 [M-105$^+$] (20%, metastable 209·5). [Found: C, 75·2; H, 4·7; N, 4·4 $C_{20}H_{15}NO_3$ requires: C, 75·7; H, 4·8; N, 4·4%].

Isolation of **19**. Evaporation of the acetone mother-liquor from which **18** separated gave a residue (0·4 g), which was repeatedly chromatographed upon alumina, eluting with chloroform:benzene (1:1). Eventually a small amount (10 mg) of crystalline material was isolated; recrystallisation from chloroform/benzene gave colourless prisms, m.p. 127–129°; λ_{max} nm, 250, 296, 320; ν_{max} cm^{-1}, 3400 (—NHCO Ar), 1710 (—CO_2Me), 1650 (—NHCO Ar). NMR ($CDCl_3$): 8·6–7·1 m [10] (aromatic protons). 5·3 broad doublet [1] (—N$\underline{H}$CO—, removed by prolonged deuteration); 3·5 s [3] (—$CO_2C\underline{H}_3$), 2·6 d [3] (—NHCOC$\underline{H}_3$) J = 7 Hz, collapses to singlet on prolonged deuteration); mass (*m/e*) 319 [M^+] (75%), 251 (100%), 230 (35%), M^+ = 319·1210, $C_{20}H_{17}NO_3$ requires: 319·1208.

Potassium ferricyanide degradation of **9**

The maleic anhydride adduct, from experiment (a) above, (0·15 g) was dissolved in a soln of K_2CO_3 (1 g) in water (50 ml) (complete soln requires approximately 30 min) and treated with potassium ferricyanide (2 g) in water (10 ml). After 5 hr at room temp the soln was acidified and stored at 0° for several days. The fine ppt which had then formed was collected and recrystallised from benzene to give 2-methoxy carbonylphenanthridone as needles (10 mg) m.p. 221–222° (lit.[21], 223–224°; ν_{max} cm^{-1}, 1715 (—CO_2Me), 1645 (ArCO$\underset{|}{N}$—); NMR ($CDCl_3$) 8·9 d [1] (C_7—$\underline{H}$). 8·6–7·2 m [6] (aromatic protons). 3·9 s [3] (—OC$\underline{H}_3$), 3·78 s [3] (—$\underset{|}{N}$—C$\underline{H}_3$). [Found: C, 71·6; H, 4·6; N, 5·0 calc. for $C_{16}H_{13}NO_3$; C, 71·9; H, 4·9; N, 5·2%].

4-Vinylisoquinoline (7, R = H)

Methyltriphenylphosphonium bromide (2·5 g) suspended in ether (100 ml) was treated with BuLi (1 g) in ether (50 ml), the mixture being protected by an atmosphere of N_2. After stirring for 15 min isoquinoline-4-aldehyde (1 g) in ether (50 ml) was introduced, and the suspension stirred at room temp for 20 hr. Solids were then removed and the filtrate was worked up for basic material to yield (0·46 g) (45%) of almost pure **7** (R = H) as a pale red oil; ν_{max} ~900 cm^{-1} ($\diagdown$C=CH$_2$).

β-Ethyl-[4-isoquinolyl]acrylate (7, R = CO_2Et)

A mixture of isoquinoline-4-aldehyde (0·1 mol) and carboethoxymethylenetriphenylphosphorane (0·1 mol) was heated under reflux with benzene for 4 hr. After cooling, the mixture was extracted with 2N HCl and the combined extracts were basified (Na_2CO_3) and extracted with ether. The ethereal soln was washed with water, saturated $NaHSO_3$ aq, water and dried. Evaporation left **7**, (R = CO_2Et) as a red oil, which was characterised as the methiodide m.p. 159–160°, yield 75%; ν_{max} cm^{-1}, 1710 (—CO_2Et), 1640 ($\diagdown$C=$\overset{+}{\underset{|}{N}}$—Me), 1610 ($\diagdown$C=C$\diagup$); NMR ($CF_3CO_2H$) 9·7 s [1] ($C_1$—$\underline{H}$), 9·0–8·0 m [6] (aromatic protons, C_3—$\underline{H}$ and one olefinic proton), 6·9 d [1] J = 16 Hz (olefinic proton). 4·7 s [3] ($\underset{|}{\overset{|}{N^+}}$—C$\underline{H}_3$). 4·5 q [2] J = 7 Hz ($CO_2C\underline{H}_2$—CH_3), 1·5 t [3] J = 7 Hz (CO_2—CH_2—C$\underline{H}_3$). [Found: C, 48·5; H, 4·5: N, 4·0; I, 34·0 $C_{15}H_{16}NO_2I$ requires: C, 48·7; H, 4·4; N, 3·8; I, 34·3%].

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1,2-DIHYDROISOQUINOLINES

INDENO[1,2-c]ISOQUINOLINE DERIVATIVES

(Tetrahedron, 1971, 27, 281)

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1,2-DIHYDROISOQUINOLINES—XVI[1]

INDENO[1,2-*c*]ISOQUINOLINE DERIVATIVES

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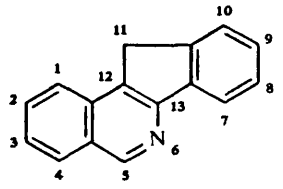
Abstract—The preparation of indeno[1,2-*c*]isoquinolines by three methods is described, and some earlier literature concerning the cyclization of 2-methyl-4-benzyl-1,2-dihydroisoquinolines corrected.

RECENTLY, in a re-investigation of some of Perkin's work[2] with the alkaloid cryptopine, we[3] showed that epicryptopirubin chloride is a derivative of 11*H*-indeno [1.2-*c*]isoquinoline (**1**), and during attempts to synthesise some benzo[*c*]phenanthrides, we[4] described a further example of this ring-system. The only other reports concerning indeno[1.2-*c*]isoquinoline derivatives are those of Chatterjea and Mukherjee[5] and of Wawzonek *et al.*[6] Since isocoumarins are easily converted into isocarbostyrils,[7] the closely related indeno[1.2-*c*]isocoumarins[7, 8] can be regarded as synthetic precursors of derivatives of **1**.



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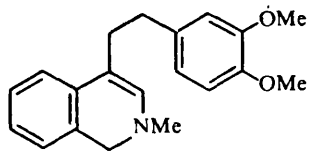

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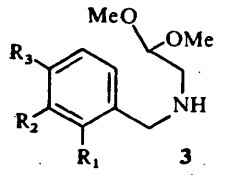
In view of our interest in indeno[1.2-*c*]isoquinolines, and of our considerable interest in 4-benzylisoquinolines,[9] we were intrigued by the report[10] that certain 2-methyl-4-benzyl-1,2-dihydroisoquinolines are cyclized to 5.6.12.13-11*H*-tetrahydroindeno[1.2-*c*]isoquinolines by acids, especially since we[11] had found that the 2-methyl-4-[β-arylethyl]-1,2-dihydroisoquinoline (**2**) undergoes disproportionation, and not ring-closure under similar conditions. Gensler *et al.*[10] reported that acid-catalysed condensation of **3**, ($R_1 = R_2 = OMe$; $R_3 = H$) with piperonal initially gave a compound formulated as **4**, in agreement with our[12] previous suggestion, and that this was converted by alkali into the 4-benzylisoquinoline **5**; hydrochloride m.p. 100–102°). A small amount of the 11-*H*-indeno[1.2-*c*]isoquinoline (**6**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) was also isolated. Gensler's structural assignments were based essentially upon NMR evidence. The methiodide of **5** was reduced with LAH to the stable 1,2-dihydroisoquinoline (**7**), which was then treated with a HCl/acetic acid mixture. The product, an oil, was allocated[10] structure **8** (R = H) on the basis of spectral data and the dehydrogenation of it with iodine to a quaternary

iodide, said to be identical with **9**, the methiodide of **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$).

In our hands,[13] the condensation of **3** ($R_1 = R_2 = OMe$; $R_3 = H$) with piperonal gave a small amount of the hydrochloride of **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) as described by Gensler *et al.*, but the major product, a hydrochloride m.p. 100–102°, was found[14] to be **10** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$), which is easily isomerised by base to **5**, methiodide m.p. 178–180°. When the 1,2-dihydroisoquinoline (**7**) was treated with HCl/acetic acid as previously[10] described, disproportionation, and not ring-closure, occurred. The two products, isolated in almost equal amounts, were shown to be the metho salt of **5** and the 1,2,3,4-tetrahydroisoquinoline (**11**). The latter substance, an oil, was characterized as the methiodide, an authentic sample of which was obtained by the catalytic reduction of **7** followed by treatment with methyl iodide. An authentic sample of **8** (R = H; a solid m.p. 156–157°) was prepared by reducing **9** with $NaBH_4$, and it was found not to be identical with the base obtained by treating **7** with acids.



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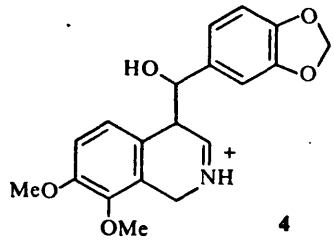

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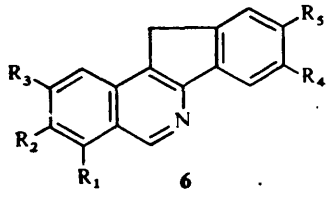

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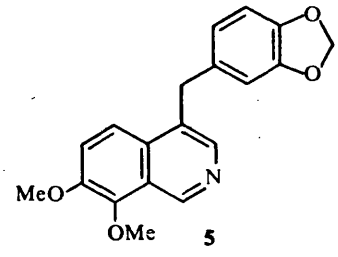

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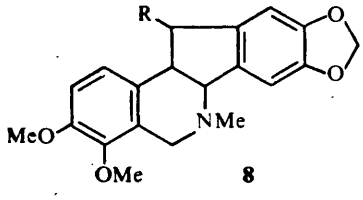

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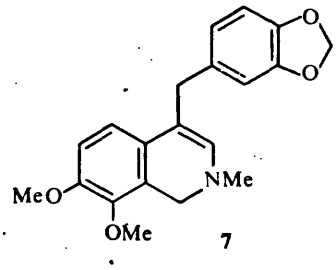
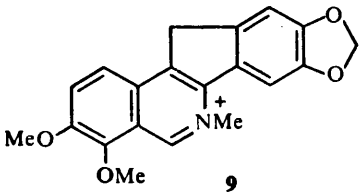


7

An analogous sequence of reactions has been conducted by us with **3** ($R_1 = H$; $R_2 = R_3 = OMe$) and piperonal. The indenoisoquinoline (**6**, $R_1 = H$; $R_2 = R_3 = OMe$; $R_4 + R_5 = CH_2O_2$) was obtained, in very small yield, but again the major product was the exocyclic compound **10** ($R_1 = H$; $R_2 = R_3 = OMe$; $R_4 + R_5 =$

CH_2O_2). When the aminoacetal **3** (R_1 = H; R_2 = R_3 = OMe) was condensed with veratraldehyde under slightly different conditions (Experimental) the 11*H*-indeno [1.2-*c*]isoquinoline (**6**, R_1 = H; R_2 = R_3 = R_4 = R_5 = OMe) was isolated easily in 21% yield. When piperonal and **3** (R_1 = H; R_2 = R_3 = OMe) were condensed under these same conditions **6** (R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2) was recovered in 17% yield. In another variation of this potentially useful reaction, the



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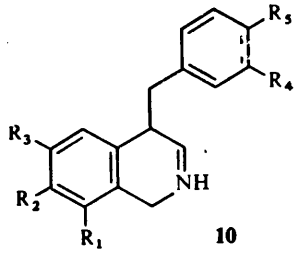

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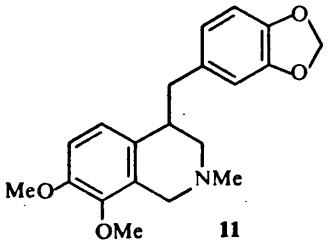

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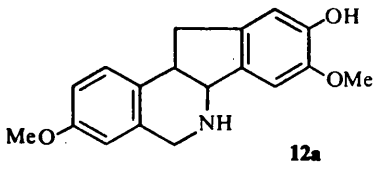
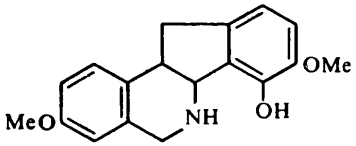


12a



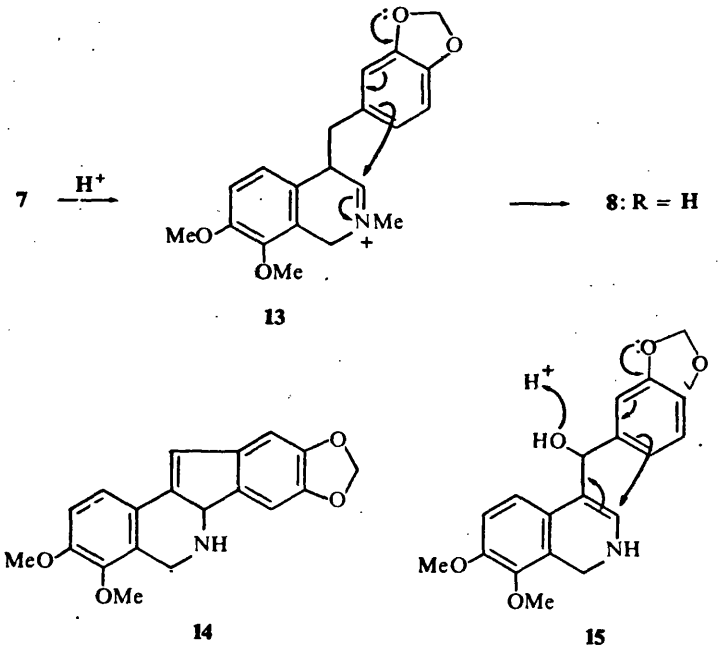
12b

compound **10** (R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH), obtained by condensing isovanillin with *m*-methoxybenzylaminoacetal (**3**, R_1 = R_3 = H; R_2 = OMe), was hydrogenated in glacial acetic acid solution, using Pd/C as catalyst. The product, isolated in 58% yield, proved to be the tetrahydroindeno[1.2-*c*]isoquinoline (**12a**) or (**12b**), and not the expected 1,2,3,4-tetrahydroisoquinoline. The formation of **12** probably involves initial attack by the relatively highly nucleophilic aromatic ring of **10** (R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH) *para* or *ortho* to the OH group at C_3 on the 1,4-dihydroisoquinolinium ring, followed by reduction of the stilbenoid double bond.

The structures of the 11*H*-indenoisoquinolines (**6**) were established by their characteristic UV, NMR and mass spectra.

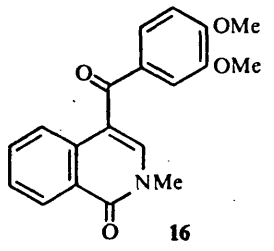
The cyclization of 4-benzyl-1,2-dihydroisoquinolines such as **7** to **8** (R = H) is most easily explained by protonation at C_4 to give the 1,4-dihydroisoquinolinium salt (**13**), followed by nucleophilic attack at C_3 by the aromatic ring of the C_4–substituent. For 1,2-dihydroisoquinolines that lack a C_4–substituent, such a protonation occurs as the

initial step as required for pavine[15] or berbine[16] formation, or rearrangement.[17] However, in a 4-benzyl-1,2-dihydroisoquinoline, it is likely that protonation occurs predominantly at nitrogen, leading to disproportionation. The formation of **6** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) in the original condensation of **3** (R_1 = R_2 = OMe: R_3 = H) with piperonal is easily understood because the first-formed product (**4**) already possesses the imminium ion structure required for cyclization; both dehydration to **10** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) and cyclization to **8** (R = OH) can then occur. Dehydration of the latter to **14** followed by isomerization and aerial oxidation completes the formation of the 11*H*-indeno [1.2-*c*]isoquinoline. A precedent for the last step already exists.[3] We were unable to cyclise **10** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) to **14** and thence to **6** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) under a variety of conditions of acid treatment, but another sequence to explain the latter's formation might involve the conversion of **4** to **15**, followed by elimination of water to give **14** and eventual oxidation to **6** as before.



We have been able to devise a new synthesis of the indeno[1.2-*c*]isoquinoline ring system based upon this last hypothesis. The 4-acylisocarbostyril[18] (**16**) was reduced with $NaBH_4$ to the alcohol (**17**, R = H; Z = O), and the derived ethyl ether (**17**, R = OEt; Z = O) was reacted with an ethanolic solution of HCl. A new, neutral compound, isolated in 88% yield, was shown by mass spectral analysis to be $C_{19}H_{17}NO_3$. The NMR spectrum of this material was found to be characteristic of the expected structure **18**. The alcohol **17** (R = H; Z = O) also cyclised to **18**, though somewhat

less readily. When an attempt was made to reduce **16** to **17** (R = H; Z = 2H) with LAH, the product was the 4-benzylidene-1,2-3,4-tetrahydroisoquinoline (**19**).



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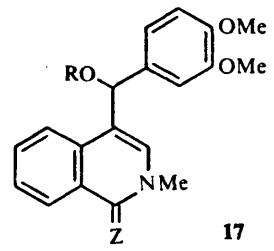

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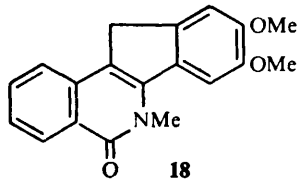

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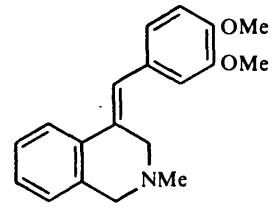


19

Acknowledgements—We thank the British Empire Cancer Campaign for Research for financial support for some of this work, the SRC for a research studentship (to M. N. Palfreyman) and Mr. K. N. Kilminster for the experimental work with (10, $R_1 = R_3 = H$; $R_2 = R_5 = OMe$; $R_4 = OH$).

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln. IR spectra were recorded as Nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

3,4-Dimethoxy-8,9-methylenedioxy-11H-indeno[1.2-c]isoquinoline (**6**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$)

Piperonal (3 g) in EtOH (15 ml) was added to 2,3-dimethoxybenzylacetaldehydedimethylaminoacetal (2·85 g) in conc HCl (15 ml). After heating at reflux for 30 min and cooling overnight, red crystals separated (2·0). A sample of this material was recrystallized from EtOH to yield **10** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) as prisms m.p. 100–102°.

The remainder of the crude product was stirred in water and the pH raised to > 10 by the addition of 30% KOHaq. After 1 hr the product was collected and heated with EtOH; the bulk of the solid readily dissolved, but some (~ 5%) remained insoluble. This was filtered off and recrystallized from pyridine to give **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) m.p. 242–243° (lit.,[10] 242–243·5, λ_{max} (ε) nm, 236 (35,000), 337 (24,000). ν_{max} cm^{-1}. 1620 (C=N), 1570 (C=C), NMR (CF_3CO_2H) ppm, 9·4 m [1] (C_5—H), 8·1–7·1 m [4] (aromatic protons), 6·1 s [2] (—OCH_2O), 4·1 m [8] (2 × OCH_3, —CH_2Ar.), Mass (*m/e*) 321 M^+ (100%), 306 M^+—CH_3 (36%), 278 (38%), 263 (20%), 248 (8%), 233 (10%), 220 (5%), 205 (15%), 177 (12%). [Found: C, 71·1; H, 4·8; N, 4·3; Calc. for $C_{19}H_{15}NO_4$. C, 71·0; H, 4·7; N, 4·4%]. This compound was further characterized as the methosulphate; colourless prisms m.p. 247–248° (EtOH). [Found: C, 56·3; H, 4·9; N, 3·4; S, 6·7. $C_{21}H_{21}NO_8S$ requires: C, 56·4; H, 4·7; N, 3·1; S, 7·2%]. Anion exchange yielded the methiodide **9**, which recrystallized as yellow needles from EtOH m.p. 253–254° (sinters at ~190°). [Found: C, 51·5; H, 3·4; N, 3·1; I, 28·6 $C_{20}H_{18}NO_4I$ requires: C, 51·8; H, 3·9; N, 3·1; I, 28·8%].

Reduction of the methosulphate or methiodide with $NaBH_4$ in EtOH gave **8**, (R = H) (87%) as colourless prisms m.p. 156–157°, from EtOH; NMR ($CDCl_3$) ppm, ~6·8 m [4] (aromatic protons), 5·9 s [2] (—OCH_2—O—), 4·2–2·9 complex [12] (2 × —OCH_3, —N—CH_2—, ArCH_2—, 2 × C$\underline{H}$—), 2·36 s [3] (—N—CH_3). [Found: C, 70·4; H, 6·2; N, 4·0. $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 4·1%].

4-(3,4-Methylenedioxybenzylidene)-7,8-dimethoxy-1,4-dihydroisoquinoline (**10**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$).

On cooling the ethanolic soln. of the major component in the above reaction, colourless plates (1·3 g) of 4-(3,4-methylenedioxybenzylidene)-7,8-dimethoxy-1,4-dihydroisoquinoline were obtained which recrystallized from EtOH; m.p. 106–108°. λ_{max} (ε) nm, 255 (48,500); ν_{max} cm^{-1}, 1620 (C=N), 1600 (C=C); NMR ($CDCl_3$) ppm, 8·6 m [1] (C_3—H), 7·4–6·5 m [6] (olefinic and aromatic protons) 5·8 s [2] (—OCH_2O—), 5·0 s [2] (>N—CH_2—), 3·9 s [6] (2 × —OCH_3). [Found: C, 70·8; H, 5·4; N, 4·2 $C_{19}H_{17}NO_4$ requires: C, 70·6; H, 5·3; N, 4·3%].

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxyisoquinoline (5)

The base (1·0 g), from the previous reaction, was heated with EtOH (10 ml) containing 30% KOH aq (25 ml) for 30 min. On cooling, colourless crystals of **5** separated (0·8 g), m.p. 115–117° (lit.,[10] 124–125°). λ_{max} (ε) nm, 236 (55,000), 286 (13,800), 340 (10,500); ν_{max} cm^{-1}, 1620 (C=N), 1570, 1500 (C=C); NMR ($CDCl_3$) ppm, 9·0 s [1] (C_1—H), 8·25 s [1] (C_3—H) ~7·0 [5] (aromatic protons), 5·8 s [2] (—OCH_2O—), 4·13 s [2] (—CH_2—Ar), 4·0 s [6] (2 × —OCH_3). [Found: C, 70·0; H, 5·2; N, 4·4. Calc. for $C_{19}H_{17}NO_4$; C, 70·6; H, 5·3; N, 4·3%]. The methiodide was also prepared: m.p. 178–180° (EtOH). [Found: C, 51·9; H, 4·5; N, 3·0; I, 27·3 $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·1; I, 27·3%].

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxy-2-methyl-1,2-dihydroisoquinoline (7)

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium iodide (2 g) was suspended in dry ether (20 ml) under N_2. LAH (1·5 g) was added portionwise, and the mixture stirred at RT for 3 hr. After this time excess LAH was destroyed by the cautious addition of 30% aqueous sodium potassium tartrate soln, and the solvent layer then decanted from the gelatinous ppt which had formed. Evaporation of the solvent yielded **7** as a crystalline residue which recrystallized from EtOH as colourless needles (1 g), m.p. 97–98° (lit.,[10] 97–98°); λ_{max} (ε) nm, 297 (10,000), 325 (18,000); ν_{max} cm^{-1}, 1640 (C=C), 1250 (—OCH_2O—), NMR ($CDCl_3$) ppm, 6·8 m [5] (aromatic protons), 5·8 s [3] (—OCH_2O— and C_3—H), 4·2 s [2] (—CH_2—N<), ~3·7 two s [6] (2 × —OCH_3), 3·3 s [2] (—CH_2—Ar), 2·67 s [3] (=N—CH_2). [Found: C, 70·4; H, 5·8; N, 4·5 Calc. for $C_{20}H_{21}NO_4$: C, 70·8; H, 6·2; N, 4·1%].

The same product (**7**) was also obtained when the above isoquinolinium salt was reduced with $NaBH_4$ in boiling absolute EtOH soln, yield 70% m.p. 97–98°.

Action of acids upon **7**

(a) *Perchloric acid.* The 1,2-dihydroisoquinoline (1 g) in EtOH soln (20 ml) containing perchloric acid (2 ml) was heated under reflux for 30 min. On cooling yellow crystals of 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium perchlorate (0·6 g) separated, m.p. 187°; λ_{max} (ε) nm, 257 (35,000); ν_{max} cm^{-1}, 1650 (C=$\overset{+}{N}$), 1080 $(ClO_4)^-$. NMR (CF_3CO_2H) ppm, 9·5 s [1] (C_1—H), 8·05 s [2] (C_5—H, C_6—H), 7·9 s [1] (C_3—H), 6·8 s [3] (aromatic protons), 5·9 s [2] (—OCH_2O—), 4·5 s [5] (—CH_2—Ar, —$\overset{+}{N}$—CH_3), 4·3, 4·2 s [6] 2 × —OCH_3). [Found: C, 54·6; H, 4·5; N, 3·8; Cl, 8·9. $C_{20}H_{20}NO_8Cl$ requires: C, 54·8; H, 4·6; N, 3·2; Cl, 8·1%].

Basification of the mother liquor with NH_4OH aq, followed by extraction with $CHCl_3$ yielded, after removal of the solvent, **11** (0·3 g) as an oil. The methiodide of this substance was prepared, affording pale yellow needles m.p. 216° (EtOH); λ_{max} (ε) nm, 288 (4830), ν_{max} cm^{-1}, 1600 (C=C); NMR (CF_3CO_2H) ppm, 7·33 q [2] J = 8 Hz (C_5—H, C_6—H); 6·8 s [3] (aromatic protons); 6·0 s [2] (—OCH_2O—); 4·67 broad s [2] (—$\overset{+}{N}$—CH_2—); 4·1–2·67 complex [17] (2 × —OCH_3, 2 × —N^+—CH_3, —CH_2—CH—CH_2—Ar). [Found: C, 52·2; H, 5·3; N, 3·1; I, 26·6. $C_{21}H_{26}NO_4I$ requires: C, 52·3; H, 5·4; N, 2·9; I, 26·3%].

This product was identical with a sample prepared by the catalytic reduction of **7** in EtOH solution at 1 atm pressure, catalyst 10% Pd/C, followed by treatment with MeI.

Oxidation of the 2-methyl-1,2,3,4-tetrahydroisoquinoline with I_2/KOAc in ethanol gave 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium iodide m.p. 180–181° identical with an authentic sample.

(b) *Hydrochloric acid/acetic acid.* The 1,2-dihydroisoquinoline (1 g) was heated under reflux with glacial

AcOH (30 ml) and conc HCl (1·5 ml) under N_2. The reaction mixture was cooled and basified with ammonia soln; extraction with $CHCl_3$ yielded **11** (50%) as an oil, which was subsequently characterized as the methiodide. The aqueous phase after $CHCl_3$ extraction was treated with 60% aq $HClO_4$ (5 ml); on cooling 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium perchlorate (44%) separated.

4-(3,4-Methylenedioxybenzyl)-6,7-dimethoxyisoquinoline

Piperonal (3 g) in EtOH (15 ml) was added to a soln of N-3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (2·85 g) in conc HCl (15 ml). After heating under reflux for 30 min the soln was cooled and allowed to stand for 12 hr. The red crystals which had separated were collected and a sample (1 g) recrystallized from EtOH, to yield **10** (R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2) (0·9 g) m.p. 140–142°; λ_{max} (ε) nm, 278 (15,300), 360 (15,300); ν_{max} cm^{-1}, 1645 (C=$\overset{+}{N}$), 1610 (C=C). NMR (CF_3CO_2H) ppm, 9·0 m [1] (C_3—H), 8·3 m [1] (CH—Ar), 7·4–6·9 [5] aromatic protons). 6·1 s [2] (—OCH_2O—), 5·2 s [2] (—N—CH_2—). 4.0 s [6] (2 × —OCH_3). [Found: C, 62·7; H, 5·9; N, 3·4; $C_{19}H_{17}NO_4$ requires: C, 62·1; H, 6·0; N, 3·4%]. The remainder of the crude product (3·5 g) was suspended in water (300 ml) and the pH raised to 10 by the addition of 30% NaOH aq. After stirring for 1 hr at RT the solid material was collected, and then recrystallized from EtOH* to yield 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline (1·8 g) as colourless needles m.p. 139–140°; λ_{max} (ε) nm, 243 (10,400), 293 (1650); ν_{max} cm^{-1}, 1620 (C=N); NMR ($CDCl_3$) ppm, 8·93 s (C_1—H) [1]; 8·25 s (C_3—H) [1]; 7·1–6·5 m [5] (aromatic protons); 5·8 s [2] (—OCH_2O—), 4·1 s [2] (ArCH_2—); 3·93, 3·83 s [6] (2 × —OCH_3). [Found: C, 70·4; H, 5·2; N, 4·5. $C_{19}H_{17}NO_4$ requires: C, 70·6; H, 5·3; N, 4·3%].

2,3-Dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinoline (6, R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2).

In the above preparation at the stage of recrystallization of the 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline*, whilst the bulk of the impure product dissolved in the hot EtOH, some material (0·2 g) was found to be insoluble. This compound was subsequently recrystallized from pyridine to yield the corresponding indenoisoquinoline, as pale yellow micro crystalline prisms m.p. 266–268°; λ_{max} (ε) nm, 243 (33,400), 276 (33,400), 330 (23,000), ν_{max} cm^{-1}; 1620, 1590 (C=C) NMR (CF_3CO_2H) ppm, 9·0 d [1] (C_5—H), 7·6, 7·5 s [2] (C_1—H, C_4—H), 7·37 and 7·2 s [2] (C_7—H, C_{10}—H), 6·1 s [2] (—OCH_2O—), 4·2 broad s [8] (2 × —OCH_3, ArCH_2—). [Found: C, 71·2; H, 4·7; N, 4·5. $C_{19}H_{15}NO_4$ requires: C, 71·0; H, 4·7; N, 4·4%].

4-(3,4-Methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline

This compound was prepared in the usual way from the corresponding methiodide (91%). Recrystallization from EtOH afforded colourless needles m.p. 82–84°; λ_{max} (ε) nm, 295 (11,300), 335 (22,600); γ_{max} cm^{-1}, 1645 (C=C), 1600 (C=C); NMR ($CDCl_3$) ppm, 6·8 m [5] (aromatic protons); 5·8 s [3] (—OCH_2O + C_3—H); 4·0 s [2] (—CH_2—N=); 3·7 s [6] (2 × —OCH_3); 3·33 s [2] (ArCH_2—); 2·67 s [3] (—N—CH_3). [Found: C, 70·6; H, 6·2; N, 4·2. $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 4·1%].

Action of acid upon 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline

The 1,2-dihydroisoquinoline was treated with AcOH and HCl as previously described, yielding 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (46%), as an oil, together with 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methylisoquinolinium perchlorate (40%) m.p. 179–181°. [Found: C, 54·4; H, 4·6; N, 3·6; Cl, 8·7. $C_{20}H_{20}NO_8Cl$ requires: C, 54·8; H, 4·6; N, 3·6; Cl, 8·1%]. The tetrahydroisoquinoline was characterised as the methiodide m.p. 248–250° (EtOH). [Found: C, 52·4; H, 5·4; N, 2·9; I, 26·0 $C_{21}H_{26}NO_4I$ requires: C, 52·3; H, 5·4; N, 2·9; I, 26·3%]. It was further oxidised with iodine/KOAc in ethanol to 4-(3,4-methylenedioxybenzyl-6,7-dimethoxy-2-methylisoquinolinium iodide (m.p. and mixed m.p. with authentic sample 203–205°), yield 90%. [Found: C, 51·6; H, 4·5; N, 3·2; I, 26·9. $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·0; I, 27·3%].

3,4,8,9-Tetramethoxy-11H-indeno[1,2-c]isoquinoline (6, R_1 = H, R_2, R_3, R_4, R_5 = OCH_3)

The aminoacetal **3** (R_1 = H, R_2 = R_3 = OCH_3), (5·1 g) and veratraldehyde (6·6 g) were treated with conc HCl (30 ml) and heated at 100° for 3 hr. After cooling the mixture was washed with ether (3 × 50 ml) and basified with 2N NH_4OH. The liberated basic material was extracted into chloroform (3 × 50 ml) and the combined extracts evaporated to yield a gum. This material in ether was treated with HCl and the solid hydrochloride which formed was collected and recrystallized from MeOH pale cream needles m.p. 268–270°, yield 21%; λ_{max} (ε) nm, 235 (32,200), 275 (36,400), 327 (20,500). ν_{max} cm^{-1}, 1620, 1580. [Found: C, 64·3;

H, 5·4; N, 3·75; Cl, 9·5. $C_{20}H_{20}NO_4Cl$ requires: C, 64·3; H, 5·4; N, 3·8; Cl, 9·5%]. Under similar conditions piperonal and the acetal (3, R_1 = H, R_2 = R_3 = OCH_3) gave a solid product; this was recrystallized from pyridine to give 6, (R_1 = H, R_2 = R_3 = OMe, R_4 + R_5 = CH_2O_2) as pale yellow prisms, m.p. 266–268°. (Yield 17%, identical with the material obtained earlier.)

4-(3-Hydroxy-4-methoxybenzylidene)-7-methoxy-1,4-dihydroisoquinoline

The acetal 3, (R_1 = R_3 = H; R_2 = OCH_3; 5 g) in 50% HCl aq (25 ml) and EtOH (10 ml) were heated to 60° and isovanillin (5 g) in EtOH (10 ml) was added. The temp of reaction was then increased to 90° and was maintained for 2 hr. After this time the volume was decreased to 50% by distillation under reduced pressure; the mixture was then allowed to cool and the solid product collected. This material (10, R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH) was virtually insoluble in all common solvents except glacial AcOH and pyridine. Recrystallization was not achieved. The free base was liberated by treating a fine suspension of the hydrochloride salt in water with ammonia. This material was recrystallized with difficulty from EtOH as colourless prisms m.p. 197–198°; λ_{max}nm, 266, 343, ν_{max} cm^{-1}, 3550 (w), 3250 (s), 2500 (w), 1610; NMR (CF_3CO_2H) ppm, 9·2–8·6 m [1]; 7·8 d [1], J = 10 Hz (C_5—H): 7·2–6·9 m [6] (olefinic and aromatic protons); 5·1–4·7 m [2] ($ArCH_2$—), 3·95 s [6] (2 × —OCH_3). Mass (*m/e*) 295 M^+ (100%), 280 M^+—15 (25%). [Found: C, 73·0; H, 5·6; N, 4·3. $C_{18}H_{17}NO_3$ requires: C, 73·2; H, 5·8; N, 4·7%].

3,10-Dimethoxy-9-hydroxy-5,6,12,13-tetrahydro-11H-indeno[1.2-c]isoquinoline (12)

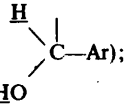
The base (10 g), prepared as in the above experiment, in glacial AcOH (150 ml) was hydrogenated at 4 atm pressure over 10% Pd/C (0·2 g) for 12 hr. Solvent and catalyst were removed to yield a yellow solid. This material crystallized from N,N'-dimethylformamide as colourless prisms (6 g) m.p. 238–239° (dec). Further purification was achieved by sublimation (200–210°; 0·2 mm); λ_{max}nm; 220, 285; ν_{max} cm^{-1}, 3500–3100; NMR (CF_3CO_2H) ppm, 7·3 d [2], J = 9·5 Hz (C_5—H); 7·1 – 6·8 m [4] (aromatic protons); 5·3–3·0 m [6] (aliphatic protons); 4·0 s [6] (2 × OCH_3). Mass (*m/e*) 297 M^+ (80%), 296 M^+—1 (100%), 280, (50%), 265 (30%). [Found: C, 72·7; H, 6·4; N, 4·7. $C_{18}H_{19}NO_3$ requires: C, 72·7; H, 6·4; N, 4·7%].

4[Hydroxy-(3,4-dimethoxyphenyl)-methyl]-2-methylisocarbostyril (17, R = H; Z = O)

4-(3,4-Dimethoxybenzoyl)-2-methylisocarbostyril[18] (2 g) in EtOH (100 ml) was treated with $NaBH_4$ (1 g). After 3 hr at reflux the solvent was removed and water added. Chloroform extraction yielded 17 (R = H; Z = O) as a colourless crystalline mass (1·7 g) which recrystallized from MeOH, m.p. 220–221°; λ_{max} (ε) nm, 295 (14,000); ν_{max} cm^{-1}, 3410 (—OH), 1635 (N—CO—), 1610, 1590 (C=N); NMR (CD_3SOCD_3) ppm, 8·1 m [1] (C_8—H), 7·7–6·7 complex [6] (aromatic protons), 5·8 s [2] (—CH(OH)Ar), 3·7 s [6] (2 × —OCH_3). [Found: C, 69·9; H, 6·0; N, 4·1 $C_{19}H_{19}NO_4$ requires: C, 70·1; H, 5·9; N, 4·3%].

5-Keto-6-methyl-8,9-dimethoxy-11H-indeno[1,2-c]isoquinoline (18)

(a) A soln of the isocarbostyril alcohol (1 g) (prepared in the previous experiment) in EtOH (50 ml) containing conc HCl (5 ml) was heated under reflux for 6 hr. After this time the soln was poured into water (50 ml) basified with 2N NaOH and extracted with $CHCl_3$ (3 × 40 ml). Evaporation of the solvent from the combined extract yielded a yellow oil, which upon trituration with MeOH gave 18 as a colourless solid. Recrystallization from MeOH afforded needles, yield 0·83 g (88%), m.p. 204–205°; λ_{max} (ε) nm, 295 (11,750); ν_{max} cm^{-1}, 1625 (C=O), 1605 (C=C); NMR ($CDCl_3$) ppm, 8·3 m [1] (C_4—H, 7·6–7·3 m [3] (aromatic protons) 7·0–7·2 s [2] (C_7—H, C_{10}—H), 3·9 s [6] (2 × OCH_3), 3·4 s [2] (—CH_2Ar). [Found: C, 74·5; H, 5·6; N, 4·7 $C_{19}H_{17}NO_3$ requires: C, 74·3; H, 5·6; N, 4·6%].

(b) The isocarbostyril alcohol (1 g) in chloroform (30 ml) was saturated with HCl during 15 min. Evaporation of the solvent gave a gum, which when treated with EtOH formed 17 (R = Et. Z = O) as colourless plates (0·9 g) m.p. 55–56°; λ_{max} (ε) nm, 285 (12,500). ν_{max} cm^{-1}, 1640 (C=O), 1620, 1590 (C=C); NMR ($CDCl_3$) ppm, 8·4 s [1] (C_8—H); 7·7–6·8 m [7] (); 3·6 q [2], J = 7 Hz (—CH_2—CH_3); 3·4 s [6] (2 × —OCH_3); 3·5 s [3] (—N—CH_3); 1·25 t [3], J = 7 Hz (CH_3—CH_2—). [Found: C, 71·1; H, 6·3; N, 4·3. $C_{21}H_{23}NO_4$ requires: C, 71·4; H, 6·6; N, 4·0%]. This compound when heated with ethanolic HCl soln, as in (a) above gave (18) in 72% yield.

4-(3,4-Dimethoxybenzylidene)-2-methyl-1,2,3,4-tetrahydroisoquinoline (19)

4-(3,4-Dimethoxybenzoyl)-2-methylisocarbostyril (1 g) in benzene (50 ml) was treated with LAH (1 g) in

small portions; after the addition of this reagent, the suspension was heated under reflux for 2 hr. The mixture was then cooled and the excess reagent decomposed in the usual way; decantation and evaporation of the solvent gave a gum, which crystallized upon trituration with EtOH. Recrystallization from this solvent yielded **19** as colourless needles (0·58 g) m.p. 112–113°; λ_{max} (ε) nm, 315 (21,000), ν_{max} cm^{-1}, 1630, 1600, 1575 (C=C); NMR ($CDCl_3$) ppm, 7·8 m [1] (C_5—H), 7·3–6·8 complex [7] (aromatic protons), 3·9 s [6] (2 × —OCH_3), ~3·6 complex [4] (2 × —CH_2—N—), 2·4 s [3] (—N—CH_3). [Found: C, 76·8; H, 7·2; N, 4·7. $C_{19}H_{21}NO_2$ requires: C, 77·3; H, 7·2; N, 4·7%].

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SYNTHESIS OF SANGUINARINE CHLORIDE

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1,2-Dihydroisoquinolines. Part XIII.† Synthesis of Sanguinarine Chloride

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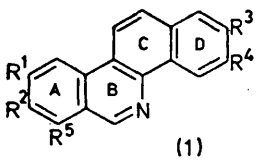
The first synthesis of sanguinarine chloride (2,3:7,8-bismethylenedioxybenzo[*c*]phenanthridine methochloride), from 2-hydroxy-3-methoxybenzaldehyde, is described.

We have previously [1] described the development of the synthetic route followed by Abramovitch and Tertzakian [2] to give the benzo[*c*]phenanthridine ring system, and outlined the preparation of the derivatives (1a—c).



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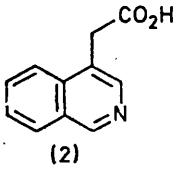
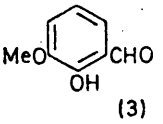


(2)

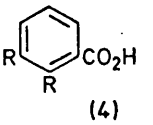
a; $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
b; $R^1R^2 = R^3R^4 = CH_2O_2$, $R^5 = H$
c; $R^1 = R^2 = OMe$, $R^3R^4 = CH_2O_2$, $R^5 = H$
d; $R^1 = H$, $R^2R^5 = R^3R^4 = CH_2O_2$
e; $R^1 = R^2 = R^3 = R^4 = R^5 = H$

The success of the method hinged upon the discovery of a simple, one-step synthesis of isoquinoline-4-acetic acid derivatives (2) from benzylaminoacetaldehyde dimethyl acetals. In principle this route to the benzo[*c*]phenanthridines should be applicable to the 2,3,7,8-tetraoxygenated compounds, as well as to the 2,3,8,9-tetraoxygenated derivatives, and we now [3] describe the first synthesis of the alkaloid sanguinarine chloride, the methochloride of the bismethylenedioxy-derivative (1d). The method called for 2,3-methylenedioxybenzaldehyde (5) as starting material. This was originally obtained by Perkin and Trikojus [4] but our preparation starts from 2-hydroxy-3-methoxybenzaldehyde (3), treatment of which with potassium hydroxide gave 2,3-dihydroxybenzoic acid (4; R = OH).

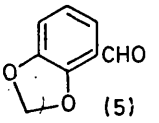
The potassium salt of (4; R = OH) was then treated with di-iodomethane to yield [5] the acid (4; RR = CH_2O_2), the acid chloride of which was reduced by the Rosenmund method to the aldehyde (5). The overall yield from (3) was 15%. The remaining steps in the



(3)



(4)



(5)

synthesis of sanguinarine chloride are summarised in Scheme 1, with optimum yields of each step indicated; the overall yield of (1d) from (3) was 0·6%. The final product, the methochloride of (1d), was identical (u.v. and i.r. spectra and mixed m.p.) with an authentic ‡ specimen of sanguinarine chloride.

It is possible to distinguish between a 2,3,8,9-tetraoxygenated benzo[*c*]phenanthridine and the isomeric 2,3,7,8-tetraoxygenated derivatives by a comparison of u.v. spectra. Thus derivatives (1b and c) show $\lambda_{max.}$ 230 and 277 nm., whereas (1d) shows $\lambda_{max.}$ 244 and 282 nm. The n.m.r. spectral data for the benzo[*c*]phenanthridines that we have synthesised are collected in the Table. The methylenedioxy-system on ring D always resonates at a lower field than that attached to ring A. The 6-proton is the one with the highest chemical shift. In each case the 11- and 12-protons resonate as an AB quartet with J 9 Hz.

The mass spectra of (1b) and (1d) are very similar, with the molecular ions as the base peaks. The fragmentation (Scheme 2) consists of a stepwise loss of HCHO and CO followed by expulsion of HCN; this

† Part XII, S. F. Dyke, M. Sainsbury, D. W. Brown, and M. N. Palfreyman, *Tetrahedron*, 1969, **25**, 5345.

‡ Obtained from Dr. J. Slavik, Institute of Medicinal Chemistry, Purkyne University, Czechoslovakia.

[1] S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, 1968, **24**, 1467.

[2] R. A. Abramovitch and G. Tertzakian, *Canad. J. Chem.*, 1963, **41**, 2265.

[3] Preliminary communication, S. F. Dyke, B. J. Moon, and M. Sainsbury, *Tetrahedron Letters*, 1968, 3933.

[4] W. H. Perkin and V. M. Trikojus, *J. Chem. Soc.*, 1926, 2925.

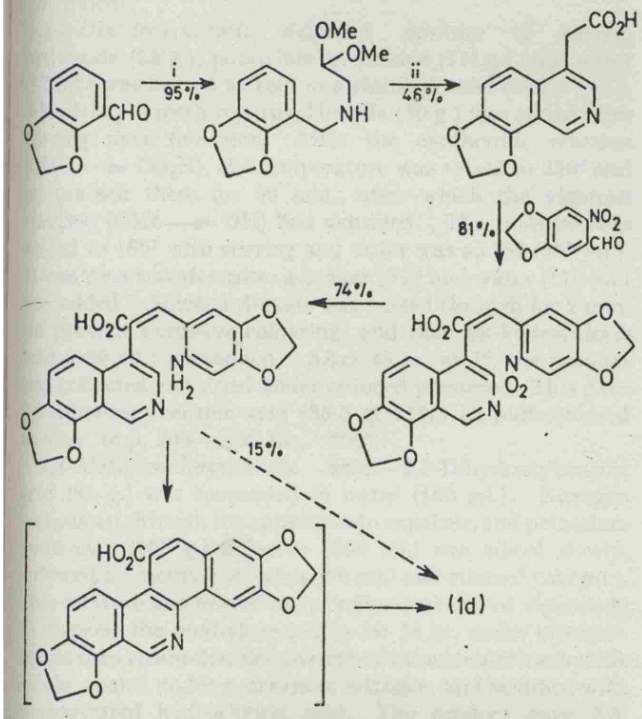
[5] W. Bonthrone and J. W. Cornforth, *J. Chem. Soc.* (*C*), 1969, 1202.

interpretation is substantiated by the appearance of the corresponding metastable ions and doubly charged species. The mass spectra of (1a) and (1c) are more

N.m.r. spectra of benzo[*c*]phenanthridines (1b—d) (p.p.m. downfield from internal tetramethylsilane; solvent trifluoroacetic acid)

	(1b)	(1c)	(1d)
H-1	7·23	7·34	7·28
H-4	7·54	7·73	8·26
H-6	9·10 (d, *J* 6 Hz)	9·30 (d, *J* 6 Hz)	9·38
H-7	7·91	8·10	
H-9			8·18 (d, *J* 10 Hz)
H-10	7·73	7·97	7·65 (d, *J* 10 Hz)
H-11	8·12 (d, *J* 9 Hz)	8·36 (d, *J* 9 Hz)	8·33 (d, *J* 9 Hz)
H-12	7·84 (d, *J* 9 Hz)	8·04 (d, *J* 9 Hz)	7·90 (d, *J* 9 Hz)
8-OMe		4·25 and 4·39	
9-OMe			
Ring D CH_2O_2	6·21	6·22	6·24
Ring A CH_2O_2	6·40		6·53

complex than those of the bis-methylenedioxy-compounds, owing to the fact that methoxy-groups can

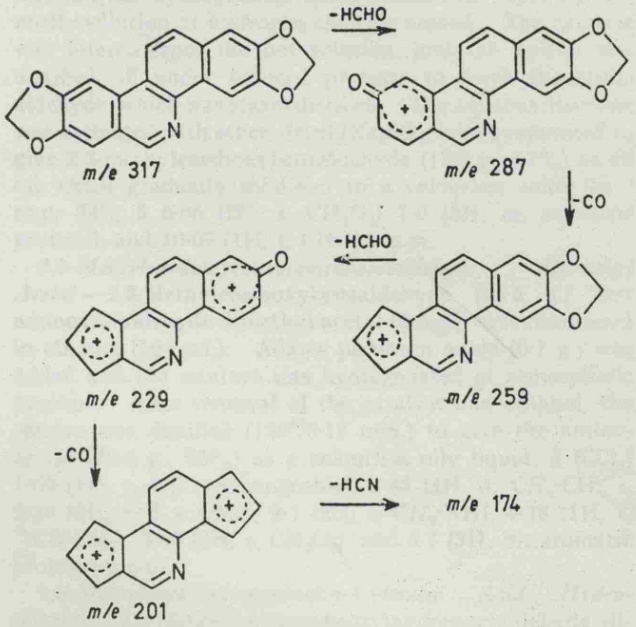


SCHEME 1 Reagents: i, (a) $H_2N{\cdot}CH_2{\cdot}CH(OMe)_2$, (b) H_2–Pt; ii, $OHC{\cdot}CO_2H$

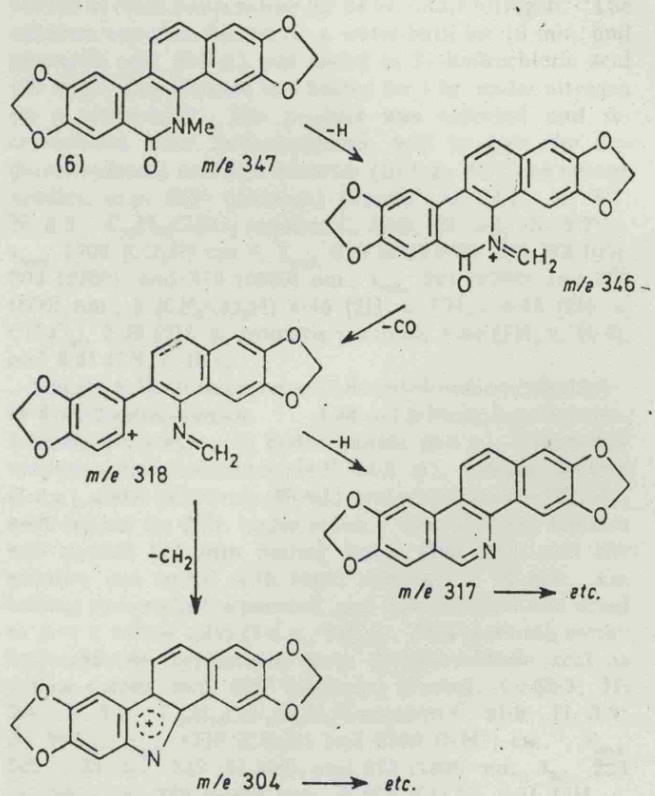
fragment in more than one way, and it has not proved possible to formulate detailed fragmentation schemes in these cases. The mass and n.m.r. spectra of some metho-salts, *e.g.* of (1d), and of some pseudo-salts derived from these, have been discussed previously.[6] The mass spectrum of oxyavicine (6) exhibits an intense (M − 1) peak (85%); this ion shows loss of CO and then of a proton. The fragmentation shown in Scheme 3 is supported by the observation of the appropriate meta-

[6] J. Slavik, L. Dolejs, V. Hanus, and A. D. Cross, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1619.

stable ions. The fragmentations of the ions at *m/e* 317 and 304 are similar to those observed for (1b); presumably similar processes are involved.



SCHEME 2

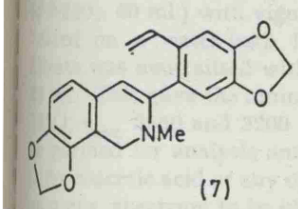


SCHEME 3

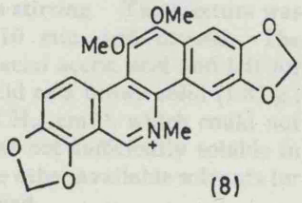
Since completion of our work, some new syntheses of the benzo[*c*]phenanthridine ring system [7,8] and a second

[7] S. V. Kessar and M. Sing, *Tetrahedron Letters*, 1969, 1155.
[8] I. Ninomiya, T. Naito, and T. Mori, *Tetrahedron Letters*, 1969, 3643.

synthesis of sanguinarine chloride, involving photolysis of anhydroprotopine (7), have been reported.[9] Some new benzo[*c*]phenanthridine alkaloids recently de-



(7)



(8)

scribed [10] contain 'extra' methoxy-groups [*e.g.* macarpine (8)]; we are currently investigating synthetic routes to them.

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol and i.r. spectra for Nujol mulls. N.m.r. spectra were recorded with a Varian A60 spectrometer; chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane. Mass spectra were recorded with an A.E.I. MS902 instrument.

2,3-*Dihydroxybenzoic Acid.*—A mixture of sodium hydroxide (28 g.), potassium hydroxide (111 g.), and water (17 ml.) was heated to 160° in a stainless steel beaker (1 l.). 2-Hydroxy-3-methoxybenzaldehyde (50 g.) was added with stirring over five min. After the exothermic reaction (CHO ⟶ CO_2H), the temperature was raised to 250° and maintained there for 30 min., after which the vigorous reaction (OMe ⟶ OH) had subsided. The mixture was cooled to 160° with stirring and water was added (330 ml.). It was then transferred to a beaker (3 l.) and water (170 ml.) was added. Sulphur dioxide was passed through for 2 min. (to prevent excessive colouring) and then 6N-hydrochloric acid (500 ml.) was added. After 48 hr. at 1°, the product was collected and dried under reduced pressure. This gave 2,3-dihydroxybenzoic acid (35·5 g, 71%) as buff-coloured needles, m.p. 200—202° (lit.,[4] 200°).

2,3-*Methylenedioxybenzoic Acid.*—2,3-Dihydroxybenzoic acid (95 g.) was suspended in water (180 ml.). Nitrogen was passed through the apparatus to expel air, and potassium hydroxide (103 g.) in water (400 ml.) was added slowly, followed by methylene iodide (50 ml.) and ethanol (250 ml.). This mixture was heated under reflux and stirred vigorously to disperse the methylene iodide for 18 hr. under nitrogen. It was then steam-distilled to remove the excess of methylene iodide, cooled under a stream of nitrogen, and acidified with concentrated hydrochloric acid. The product gave 2,3-methylenedioxybenzoic acid (44·2 g., 43%) as tan-coloured prisms, m.p. 226—227° (from ethanol) (lit.,[4] 227°). 2,3-Methylenedioxybenzoic acid (33·0 g.) was heated under reflux with thionyl chloride for 2 hr. The excess of thionyl chloride was distilled off and the crude product was distilled under reduced pressure (160°/20 mm.) to give 2,3-methylenedioxybenzoyl chloride (31·2 g., 85%), which yielded colourless needles, m.p. 116° (from xylene) (lit.,[4] 116°).

2,3-*Methylenedioxybenzaldehyde.*—2,3-Methylenedioxybenzoyl chloride (30·0 g.) was dissolved in sodium-dry xylene (500 ml.). 5% palladium–barium sulphate (3·5 g. was added, together with fresh quinoline-S catalyst poison [0·35 ml.; prepared by heating flowers of sulphur (1 g.) and quinoline (6 ml.) under reflux for 6 hr. and then diluting the product to 100 ml. with sodium-dry xylene]. The solution was hydrogenated under reflux with rapid stirring until evolution of hydrogen chloride ceased. The catalyst was filtered from the hot solution, and the xylene was distilled off under reduced pressure to leave the crude aldehyde, which was steam distilled. The aqueous distillate was extracted with ether, dried (Na_2SO_4), and evaporated to give 2,3-methylenedioxybenzaldehyde (13·9 g., 57%) as an oil which gradually solidified to a colourless solid (lit.,[4] m.p. 34°), δ 6·05 (2H, s, CH_2O_2) 7·0 (3H, m, aromatic protons), and 10·07 (1H, s, CHO) p.p.m.

2,3-*Methylenedioxybenzylaminoacetaldehyde Dimethyl Acetal.*—2,3-Methylenedioxybenzaldehyde (13·5 g.) and aminoacetaldehyde dimethyl acetal (9·5 g.) were condensed in ethanol (100 ml.). Adams platinum oxide (0·1 g.) was added and the mixture was hydrogenated at atmospheric pressure. After removal of the catalyst and ethanol, the residue was distilled (120°/0·15 mm.) to give the aminoacetal (20·5 g., 95%) as a colourless oily liquid, δ (CCl_4) 1·60 (1H, s, NH, exchangeable), 2·63 (2H, d, CH_2·CH<), 3·26 (6H, s, 2 × OMe), 3·7 (2H, s, CH_2·NH), 4·38 (1H, t, >CH·CH_2), 5·85 (2H, s, CH_2O_2), and 6·7 (3H, m, aromatic protons) p.p.m.

7,8-*Methylenedioxyisoquinolin-4-ylacetic Acid Hydrochloride.*—2,3-Methylenedioxybenzylaminoacetaldehyde dimethyl acetal (20 g.) in 6N-hydrochloric acid (400 ml.) was stirred at room temperature for 24 hr. under nitrogen. The solution was then heated on a water-bath for 10 min. and glyoxylic acid (8·5 g.) was added in 2N-hydrochloric acid (20 ml.). The mixture was heated for 1 hr. under nitrogen on a water-bath. The product was collected and recrystallised from 2N-hydrochloric acid to give the *isoquinolinylacetic acid hydrochloride* (10·3 g., 46%) as orange needles, m.p. 209° (decomp.) (Found: C, 54·1; H, 3·7; N, 5·5. $C_{12}H_{10}ClNO_4$ requires C, 53·9; H, 3·8; N, 5·2%), $\nu_{max.}$ 1700 (CO_2H) cm.$^{-1}$, $\lambda_{max.}$ 210 (ε 21,000), 240 (23,700), 302 (2200), and 379 (2500) nm., $\lambda_{min.}$ 224 (9700) and 335 (800) nm., δ (CF_3·CO_2H) 4·45 (2H, s, CH_2), 6·52 (2H, s, CH_2O_2), 7·99 (2H, s, aromatic protons), 8·44 (1H, s, H-3), and 9·61 (1H, s, H-1).

trans-4,5-*Methylenedioxy*-α-(7,8-*methylenedioxyisoquinolin*-4-*yl*)-2-*nitrocinnamic Acid.*—7,8-Methylenedioxyisoquinolin-4-ylacetic acid hydrochloride (6·0 g.), 2-nitro-4,5-methylenedioxybenzaldehyde [11] (4·2 g.), sodium acetate (1·8 g.), acetic anhydride (90 ml.), and triethylamine (60 ml.), were heated for 2 hr. under reflux. The resulting solution was poured hot into boiling water (300 ml.), and the mixture was boiled with rapid stirring for 10 min. On cooling the product separated, and was collected and dried to give a yellow solid (7·4 g., 81%). This material, as the hydrochloride, crystallised from 2N-hydrochloric acid as yellow *needles*, m.p. 238° (decomp.) (Found: C, 52·3; H, 3·4; N, 6·0. $C_{20}H_{13}ClN_2O_8,H_2O$ requires C, 51·9; H, 3·3; N, 5·8%), $\nu_{max.}$ 1710 (CO_2H) and 2580 (NH^+) cm.$^{-1}$, $\lambda_{max.}$ 209 (ε 34,100), 243 (34,500), and 373 (7600) nm., $\lambda_{min.}$ 225 (21,500) and 329 (5500) nm., δ (CF_3·CO_2H) 6·01 (2H, s, CH_2O_2 on ring D), 6·43 (1H, s, CH=C), 6·48 (2H, s, CH_2O_2 on ring A), 7·67 (1H, s, cinnamic 6-H), 7·89 (2H, s, isoquinoline 5- and 6-H), 8·21 (1H, s, isoquinoline 3-H), 8·90 (1H, s, cinnamic 3-H), and 9·52 (1H, s, isoquinoline 1-H).

[9] M. Onda, K. Yonezawa, and K. Abe, *Chem. and Pharm. Bull. Japan*, 1969, **17**, 404.

[10] J. Slavik, L. Slavikova, and K. Haisova, *Coll. Czech. Chem. Comm.*, 1967, **32**, 4420.

[11] A. H. Salway, *J. Chem. Soc.*, 1909, **95**, 1163.

trans-2-*Amino*-4,5-*methylenedioxy*-α-(7,8-*methylenedioxyisoquinolin*-4-*yl*)*cinnamic Acid*.—A hot solution of iron(II) sulphate (12 g.) in water (40 ml.) was added to a hot solution of the nitro-compound just described (2·0 g.) in ammonia (*d* 0·880; 60 ml.) with vigorous stirring. The mixture was heated on a water-bath for 10 min. and filtered. The filtrate was neutralised with glacial acetic acid and left for 24 hr. This gave the amino-acid as a brown solid (1·37 g., 74%), $\nu_{max.}$ 3350 and 3200 (N·CH_2) cm.$^{-1}$, which could not be purified for analysis and was not sufficiently soluble in trifluoroacetic acid or any of the other available solvents for an n.m.r. spectrum to be obtained.

2,3,7,8-*Bismethylenedioxybenzo*[c]*phenanthridine*.—The aforementioned amino-acid (3·0 g.) in 2N-hydrochloric acid (180 ml.) was diazotised with sodium nitrite (0·80 g.) in water (60 ml.). The excess of nitrous acid was decomposed with urea, and copper powder (3·0 g.) was added. The mixture was stirred for 5 hr. at room temperature and filtered. This product was dried under reduced pressure, and heated at 230° for 20 min. in quinoline; decarboxylation took place. Water was added and the mixture was steam-distilled to remove the quinoline (20 ml.). The solid residue was dried and extracted (Soxhlet) with chloroform for 48 hr. The chloroform was removed and the residue was sublimed (240°/0·05 mm.). Recrystallisation of the sublimate from pyridine gave 2,3:7,8-bismethylenedioxybenzo[*c*]phenanthridine (0·375 g., 15%) as pale yellow needles, m.p. 280—281° (decomp.) (Found: C, 72·1; H, 3·5; N, 4·5. Calc. for $C_{19}H_{11}NO_4$: C, 71·9; H, 3·5; N, 4·4%), $\nu_{max.}$ 1645 (C=N) cm.$^{-1}$, $\lambda_{max.}$ 215 (ε 20,100), 244 (46,300), and 282 (35,800) nm., $\lambda_{min.}$ 224 (16,800) and 265 (22,600) nm., $\lambda_{infl.}$ 295 (27,700) and 330 (15,300) nm.

Sanguinarine Chloride.—2,3,7,8-Bismethylenedioxybenzo[*c*]phenanthridine (100 mg.) was heated under reflux with dry xylene (20 ml.). Freshly distilled dimethyl sulphate (0·5 ml.) was added and the mixture was heated under reflux for 1 hr., then cooled. The orange precipitate was collected, washed with benzene and petroleum (b.p. 40—60°), and dried to give the methosulphate (121 mg.), m.p. 238—240° (decomp.). This was heated under reflux with water (20 ml.) for 15 min.; the solution was then filtered, acidified with a few drops of concentrated hydrochloric acid, and left overnight. Fine orange needles which separated gave sanguinarine chloride, m.p. 273—274° (decomp.) (from 2N-hydrochloric acid), identical with the natural product from *Sanguinaria canadensis* (mixed m.p. and i.r. and u.v. spectra). The m.p. is sensitive to the rate of heating (Found: C, 59·4; H, 4·5. Calc. for $C_{20}H_{14}ClNO_4,2H_2O$: C, 59·5; H, 4·5%), $\nu_{max.}$ 1640 (C=N) and 3340 (H_2O) cm.$^{-1}$, $\lambda_{max.}$ 277 (ε 45,100) and 330 (34,800) nm., $\lambda_{min.}$ 302 (14,600) nm.

We thank the S.R.C. for a research studentship (to B. J. M.). We also thank Dr. Slavik for the sample of the natural alkaloid.

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A SYNTHESIS OF BERBINE DERIVATIVES

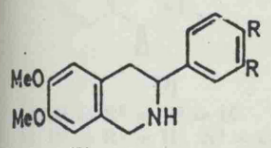
(J.Chem.Soc.C., 1971, 3219)

Aspects of Isocoumarin Chemistry. Part I. A Synthesis of Berbine Derivatives

By D. W. Brown, S. F. Dyke, M. Sainsbury and G. Hardy, School of Chemistry and Chemical Engineering, Bath University of Technology, Bath, Somerset

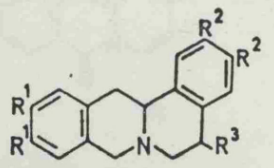
A method has been developed for the preparation of 3-arylisocoumarins, which have been utilised in efficient syntheses of 5-hydroxyberbine and of 8-oxo-5,6,13,14-dehydroberbine derivatives.

RECENTLY [1] we described syntheses of the two 5-hydroxyberbine derivatives (2a) and (2b) from the 3-aryl-1,2,3,4-tetrahydroisoquinolines (1a) and (1b), respectively. The berbines (2c) and (2d) were also obtained from the same starting materials. Most naturally occurring berbines, and the 5-hydroxyberbines berberastine and thalidastine, possess the 2,3,9,10-tetraoxygenation pattern, rather than the 2,3,10,11-orientation depicted in (2a)—(2d). The synthesis of such structures by the above method would require 3-aryl-7,8-dioxyisoquinoline derivatives as starting materials, compounds difficult to prepare by conventional methods. However, since isocoumarins can be converted into isocarbostyrils by reaction with ammonia or primary amines [2,3] and since a variety of methods exist [2] for the preparation of 3-arylisocoumarin derivatives, we hoped to utilise these oxygen heterocycles in our work. We have now established that the required berbine derivatives can be conveniently prepared from isocoumarins.



(1)

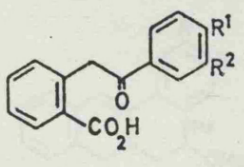
a; R = OMe
b; R + R = CH_2O_2



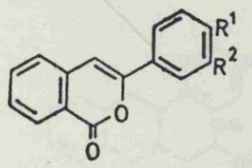
(2)

a; $R^1 = R^2 = OMe$; $R^3 = OH$
b; $R^1 = OMe$; $R^2 + R^3 = CH_2O_2$; $R^3 = OH$
c; $R^1 = R^2 = OMe$; $R^3 = H$
d; $R^1 = OMe$; $R^2 + R^3 = CH_2O_2$; $R^3 = H$
e; $R^1 = R^3 = H$; $R^2 = OMe$
f; $R^1 = H$; $R^2 = OMe$; $R^3 = OH$
g; $R^1 = H$; $R^2 + R^3 = CH_2O_2$; $R^3 = OH$

Several methods have been investigated for the preparation of the 3-arylisocoumarins (4a—f) or the corresponding keto-acids (3a—f) from which they may be obtained in a single step. A direct method for preparing 3-arylisocoumarins involves the condensation of a homophthalic acid or anhydride with a phenol in the presence of stannic chloride [3] or polyphosphoric acid.[4] We have found however that when equimolar quantities of homophthalic anhydride, veratrole, and tin(IV) chloride, are heated at 80° for 4 h, a vigorous reaction occurs to give the 2-carboxydeoxybenzoin (3c) (9%), and a phenolic keto-acid [(3d) or (3e)] (35%). No reaction occurred under less vigorous conditions, and homophthalic acid failed to react under any conditions. Homophthalic anhydride and methylenedioxybenzene reacted to give inseparable mixtures of phenolic products.



(3)



(4)

a; $R^1 = R^2 = H$
b; $R^1 = OMe$; $R^2 = H$
c; $R^1 = R^2 = OMe$
d; $R^1 = OMe$; $R^2 = OH$
e; $R^1 = OH$; $R^2 = OMe$
f; $R^1 + R^2 = CH_2O_2$

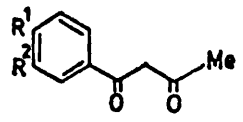
A route to 2-carboxydeoxybenzoin (3a) developed by Schnekenburger [5] involves the acylation of homophthalic anhydride with benzoyl chloride, and although we could obtain good yields of (3a) in this way, the reaction failed completely with homophthalic anhydride and 3,4-methylenedioxybenzoyl chloride.

It has been reported [6] that the keto-acid (3b) can be obtained, in 58% yield, when *o*-bromobenzoic acid is heated with 1-(4-methoxyphenyl)butane-1,3-dione (5a) in the presence of sodium ethoxide and copper powder. A similar reaction has been described [6] between 2-bromo-5-methoxybenzoic acid and ethyl acetoacetate to give the keto-acid (6) We have found that the β-diketone (5b), which was easily obtained from acetoveratrone and ethyl acetate, reacted with *o*-iodobenzoic acid, in the presence of sodium ethoxide and copper under the original conditions [6] to give the expected keto-acid (3c) (37%). The product, identical with the compound obtained earlier from homophthalic anhydride and veratrole, was easily cyclised to the isocoumarin (4c) by heat. The reaction sequence was repeated with the β-diketone (5c), but this time the product, obtained in 47% yield, proved to be the isocoumarin (4f).

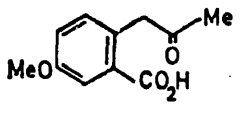
When the keto-acid (3a), or the derived isocoumarin (4a) was heated under reflux with ethanolic aqueous ammonia solution, the 3-arylisocarbostyril (7a) was produced in 28% yield, but when aminoacetaldehyde dimethyl acetal was used instead of ammonia, a high yield of a new compound ($C_{19}H_{19}NO_3$) was obtained. The spectral characteristics are entirely in accord with the

[1] D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Letters*, 1968, 5177.
[2] R. G. Barry, *Chem. Rev.*, 1964, **64**, 229.
[3] A. Rose and N. P. Buu-Hoï, *J. Chem. Soc.* (*C*), 1968, 2205 and references therein.
[4] G. N. Dorofeenko, E. V. Kuznetsov, and V. E. Ryabinina, *Tetrahedron Letters*, 1969, 711.
[5] J. Schnekenburger, *Arch. Pharm.*, 1964, **297**, 734.
[6] A. Horeau and J. Jacques, *Bull. Soc. chim. France*, 1948, 53.

expected structure (7b). Repetition of this latter reaction with (3c) gave (7c) in 88% yield. The n.m.r. and

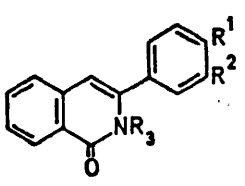


(5)



(6)

a; R^1 = OMe; R^2 = H
b; R^1 = R^2 = OMe
c; R^1 + R^2 = CH_2O_2



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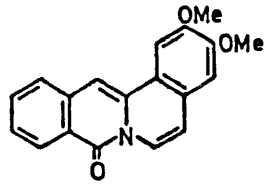
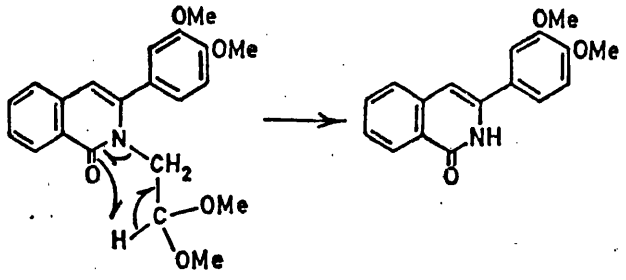


(8)

a; R^1 = R^2 = R^3 = H
b; R^1 = R^2 = H; R^3 = CH_2·CH(OMe)$_2$
c; R^1 = R^2 = OMe; R^3 = CH_2·CH(OMe)$_2$
d; R^1 = R^2 = OMe; R^3 = H
e; R^1 + R^2 = CH_2O_2; R^3 = CH_2·CH(OMe)$_2$

mass spectral data are consistent with the proposed structure. Thus, a prominent peak (*m/e* 281) is attributed to a typical McLafferty-type elimination as indicated.

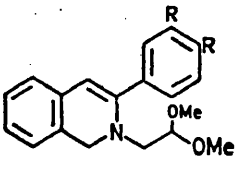


(7c) (7d)

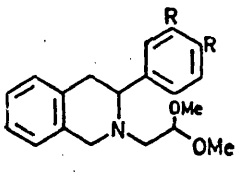
With the isocoumarin (4f) and aminoacetal, the isocarbostyril (7e) was obtained (82%). The amido-acetal (7c), dissolved in 6N-ethanolic HCl, and left at room temperature for 3 days, deposited an orange solid. Purification of this gave a yellow, neutral compound (87%), m.p. 230—231° ($C_{19}H_{15}NO_3$). The i.r. spectrum showed absorption at 1660 (CO–N) and 1615 cm^{-1} (C=C); the n.m.r. spectrum is consistent with structure (8). In particular two 1H singlets attributed to the aromatic protons on the methoxylated ring indicate that ring-closure of (7c) has occurred. The mass spectrum of the product is in full accord with an aromatic system; the only significant fragmentations occur at $M - 15$, $M - 43$, and $M - 86$. Reduction of (8) with lithium aluminum hydride in THF, followed immediately by sodium borohydride in aqueous ethanol gave 2,3-dimethoxyberbine (2e), identical with an authentic sample.[7] The overall yield of (2e) from the keto-acid (3c) was 47%, which compares favourably with previous efforts.[7]

When the amido-acetal (7c) was reduced with lithium aluminium hydride the 1,2-dihydroisoquinoline (9a) was formed, which, without isolation, was further reduced with sodium borohydride to give the 1,2,3,4-tetrahydroisoquinoline (10a) (96%). When (10a) was treated with 6N-HCl under the conditions previously described,[1] the hydrochloride of the 5-hydroxyberbine (2f) was obtained (66%). This structure was confirmed by catalytic hydrogenolysis of the compound to form 2,3-dimethoxyberbine (2e).

The isocarbostyril (7e) was then subjected to the above sequence of reactions; the 1,2,3,4-tetrahydroisoquinoline (10b), obtained *via* (9b) was cyclised to (2g); overall yields were 59%.



(9)



(10)

a; R = OMe
b; R + R = CH_2O_2

EXPERIMENTAL

U.v. spectra were determined in 95% ethanol and i.r. spectra were recorded as Nujol mulls.

1-(3,4-Dimethoxyphenyl)butane-1,3-dione (5b).—Acetoveratrone (4·0 g) in ethyl acetate (4 ml) was added to a suspension of sodium (0·6 g) in benzene (15 ml). After 16 h at room temperature the reaction mixture was poured into ether (200 ml); the sodio-derivative was collected, washed with ether, and then treated with 30% aqueous acetic acid (75 ml). A brown oil formed slowly and eventually crystallised to give (5b). The ketone recrystallised as yellow needles (3·7 g, 74%), m.p. 69—71° [from light petroleum (b.p. 60—80°)], $\nu_{max.}$ 1640—1550 cm^{-1}; $\lambda_{max.}$ (ε) 233 (8500) and 353 nm (11,950) (Found: C, 64·9; H, 6·55. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·35%). The ketone (5c) was prepared in an analogous manner in 80% yield, m.p. 86—88° (lit.,[8] 91—92°).

3,4-Dimethoxyphenyl 2'-Carboxybenzyl Ketone (3c).—(*a*) *o*-Iodobenzoic acid (2·48 g), the butane-1,3-dione (5b) (2·22 g), and copper powder (0·1 g) were added to a solution of sodium (0·5 g) in ethanol (12 ml). After 3·5 h under reflux, the reaction mixture was cooled and filtered. Evaporation of the filtrate yielded a brown residue, which was treated with 30% aqueous sodium hydroxide (25 ml) and heated on a steam-bath for 30 min. The product was then cooled extracted several times with ether, and finally acidified to yield (3c). This material was collected; crystallised as prisms (1·1 g, 37%), m.p. 189—190° (from AcOH), $\nu_{max.}$ 3050—2500, 1690, and 1675 cm^{-1}; $\lambda_{max.}$ (ε) 226 (20,000), 271 (7000), and 303sh nm (4000), δ [$(CD_3)_2SO$] 8·0—7·8 (m, 1H, 3'-H), 7·6—7·2 (m, 3H, 4-, 5-, 6-H), 7·7 (d, 1H, $J_{2,6}$ 2·5 Hz, 2-H), 7·4 (q, 1H, $J_{5,6}$ 8 Hz, $J_{2,6}$ 2·5 Hz, 6-H), 7·1 (d, 1H, $J_{5,6}$ 8 Hz, 5-H), 4·7 (s, 2H, CH_2), and 3·85, and 3·6 p.p.m. (each s, 6H, 2 × OMe) (Found: C, 68·3; H, 5·5. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·4%).

(*b*) Homophthalic anhydride (1·6 g), veratrole (1·4 g), and

[7] D. W. Brown and S. F. Dyke, *Tetrahedron*, 1966, **22**, 2429.
[8] A. Resplandy, *Compt. rend.*, 1961, **253**, 1064.

tin(IV) chloride (2·6 g) were heated at 80° for 1 h. The residue was partitioned between dichloromethane (50 ml) and 3N-HCl (50 ml); after 16 h the organic layer was separated and washed with 10% aqueous sodium hydrogen carbonate (25 ml) and water (25 ml); the dried solvent layer was then evaporated to give a brown oil (1·3 g) ($\nu_{max.}$ 3500, 1720, and 1635 cm^{-1}). This was heated at 100° with 30% aqueous sodium hydroxide (25 ml) for 30 min and then cooled, diluted, and extracted with ether. Acidification of the aqueous phase, followed by chloroform extraction, gave a resinous solid which partially crystallised on trituration with acetone to yield (3c) (0·27 g, 9%), m.p. 188—190°, unchanged on admixture with material obtained from method (*a*).

The acetone mother-liquor on evaporation gave (3d) or (3e) as a sticky brown solid which recrystallised as prisms from benzene (0·94 g, 33%), m.p. 142—144°, $\nu_{max.}$ 3520, 3050—2500, 1690, and 1675 cm^{-1}; $\lambda_{max.}$ (ε) 228 (25,300), 275 (12,100), and 305 nm (8650); δ [$(CD_3)_2SO$] 8·1—7·9 (m, 1H, 3-H) 7·8—7·1 (m, 5H, ArH), 6·95 (d, 1H, $J_{5,6}$ 8 Hz, 5-H), 4·70 (s, 2H, CH_2), and 3·85 p.p.m. (s, 3H, OMe) (Found: C, 67·1; H, 5·0. Calc. for $C_{16}H_{14}O_5$: C, 67·1; H, 4·9%).

3-(3′,4′-Methylenedioxyphenyl)isocoumarin (4f).—The butane-1,3-dione (5c) (2·0 g) was treated with *o*-iodobenzoic acid as in method (*a*) above. The aqueous solution was extracted with $CHCl_3$ (3 × 20 ml); the combined extracts washed with 10% aqueous sodium hydrogen carbonate and water, and then dried and evaporated to yield the isocoumarin (4f), as cream prisms (1·25 g, 47%), m.p. 156—157° (from MeOH), $\nu_{max.}$ 1730 and 1630 cm^{-1}; $\lambda_{max.}$ (ε) 266sh (7370), 324 (13,400), and 346sh nm (9750); δ ($CDCl_3$) 8·2 (m, 1H, 8-H), 7·7—7·2 (m, 3H, 5-, 6-, 7-H), 7·45 (d, 1H, $J_{5',6'}$ 2·5 Hz, 2′-H), 7·30 (q, 1H, $J_{5',6'}$ 10 Hz, $J_{2',6'}$ 2·5 Hz, 6′-H), 6·72 (d, 1H, $J_{5',6'}$ 10 Hz, 5′-H), 6·65 (s, 1H, 4-H), and 5·95 p.p.m. (s, 2H, O–CH_2–O) (Found: C, 72·0; H, 3·9. Calc. for $C_{16}H_{16}O_4$: C, 72·2; H, 3·8%).

Reaction between Keto-acids (3) *or Isocoumarins* (4) *with Aminoacetaldehyde Dimethyl Acetal.*—A solution of the keto-acid (or isocoumarin) (0·003 mol) and aminoacetaldehyde-dimethyl-acetal (0·01 mol) in ethanol (50 ml) was heated under reflux for 6 h. The solvent was removed and the residue was triturated with ether. Compound (7b) was obtained as a pale yellow oil (0·79 g, 85%), $\nu_{max.}$ 1650 and 1625 cm^{-1}; δ ($CDCl_3$) 8·4 (m, 1H, 8-H), 7·6—7·2 (m, 8H, ArH), 6·4 (s, 1H, 4-H), 4·8 (t, 1H, *J* 5·5 Hz, C*H*·CH_2), 4·1 (d, 2H, *J* 5·5 Hz, CH·C*H*$_2$), and 3·2 p.p.m. (s, 6H, 2 × MeO).

Compound (7c) crystallised as cream prisms (0·97 g, 88%), m.p. 134—136° (from MeOH), $\nu_{max.}$ 1650 and 1620 cm^{-1}; $\lambda_{max.}$ (ε) 293 (14,500) and 335sh nm (6450); n.m.r. spectrum very similar to that of (7b) with additional signals for two methoxy substituents [3·85 (s, 6H) replacing the signals due to 3′-H and 4′-H]; mass spectrum (70 eV) *m/e* 369 (10%), 338 (3%), 281 (23%) 75 (100%); *m/e* 213·8 (Found: C, 68·5; H, 6·4; N, 4·0. $C_{21}H_{23}NO_5$ requires C, 68·3; H, 6·3; N, 3·8%.)

Compound (7e) recrystallised from benzene as needles (0·86 g, 82%), m.p. 170—172°, $\nu_{max.}$ 1650 and 1620 cm^{-1}; $\lambda_{max.}$ (ε) 297 (12,100) and 336 nm (9700); n.m.r. spectrum similar to that of (7c) [5·9 (s, 2H, O·CH_2·O) replacing the signal at 3·85].

2,3-Dimethoxy-5,6,13,14-dehydro-8-oxoberbine (8).—The amidoacetal (7c) dissolved in 6N-aqueous ethanolic HCl (10 ml) was set aside at room temperature for 3 days. The orange solid was collected and washed with acetone; evaporation of the filtrate produced a further deposit of crystals which was combined with the first crop of material; they crystallised from 95% methanol, as vivid yellow needles (0·29 g, 87%), m.p. 230—231°, $\nu_{max.}$ 1660 and 1615 cm^{-1}; $\lambda_{max.}$ (ε) 253 (12,700), 269 (10,900), 279 (11,200), 291 (15,200), and 390 nm (7900), δ (Me_2SO) 8·3 (d, 1H, $J_{5,6}$ 8 Hz, 6-H), 8·15br (s, 1H, 9-H), 7·8 (s, 1H, 1-H), 7·7—6·9 (m, 3H, ArH), 7·6 (s, 1H, 4-H), 7·0 (s, 1H, 13-H), 6·8 (d, 1H, $J_{5,6}$ 8 Hz; 5-H), and 3·9 p.p.m. (2s, 6H, 2 × MeO); *m/e* 261 (25%); *m/e* 152·5 (Found: C, 74·95; H, 5·0; N, 4·8. Calc. for $C_{19}H_{15}NO_3$: C, 74·75; H, 4·95; N, 4·6%).

5-Hydroxy-2,3-dimethoxyberbine (2f).—A suspension of the amido-acetal (7c) (0·5 g) in anhydrous ether (50 ml) was treated with lithium aluminium hydride (1·0 g) in small portions during 1 h, at room temperature. The mixture was then heated under reflux for a further 3 h, cooled, and the excess of hydride destroyed with 30% sodium potassium tartrate solution. Evaporation of the dried ethereal solution afforded the 1,2-dihydroisoquinoline (9a) as a pale yellow oil, $\nu_{max.}$ 1610 and 1570 cm^{-1}; $\lambda_{max.}$ 340 nm. To this oil dissolved in ethanol (25 ml) was added dropwise during 15 min a solution of sodium borohydride in water (10 ml). The mixture was stirred at room temperature for 24 h; ethanol was evaporated and the aqueous suspension was extracted with ether (3 × 15 ml). The combined dried extracts were then evaporated to leave the amino-acetal derivative (10a) (0·45 g, 96%), $\nu_{max.}$ 1605 and 1595 cm^{-1}; $\lambda_{max.}$ 284 nm. Without further purification this base dissolved in 6N-HCl (25 ml) was set aside at room temperature for 48 h. The solution was washed with ether and then evaporated to dryness under reduced pressure at 40°. Addition of ethanol to the residue caused *2,3-dimethoxy-5-hydroxyberbine hydrochloride* to crystallise out (0·29 g, 66%). Recrystallisation from ethanol afforded yellow needles m.p. 205—206°, $\nu_{max.}$ 3350, 2600, and 1610 cm^{-1}; $\lambda_{max.}$ (ε) 234 (10,700) and 282 nm (3240) (Found: C, 65·4; H, 6·45; Cl, 10·5; N, 4·1. $C_{19}H_{21}NO_3$,HCl requires C, 65·6; H, 6·3; Cl, 10·2%; N, 4·0%).

5-Hydroxy-2,3-methylenedioxyberbine (2g) was prepared from (7e) by an identical procedure to that used for the dimethoxy-analogue above. Some solid material had deposited from the 6N-acid solution after 48 h, and this was combined with the product obtained by evaporation of the filtrate at 40°. Recrystallisation of the combined crops of crystals gave *5-hydroxy-2,3-methylenedioxyberbine hydrochloride* as yellow prisms [0·28 g, 59% from (7e)], m.p. 234—235°, $\nu_{max.}$ 3280 and 2520 cm^{-1} (Found: C, 64·7; H, 5·6; Cl, 10·5; N, 3·7. $C_{18}H_{17}NO_3$,HCl requires C, 65·1; H, 5·4; Cl, 10·7; N, 4·2%). The *free base*, liberated from the hydrochloride with ammonium hydroxide crystallised as pale yellow needles from ethanol, m.p. 130—131°, $\nu_{max.}$ 3300 and 2780 cm^{-1}; $\lambda_{max.}$ 238sh (6600) and 290 nm (3820); δ ($CDCl_3$) 7·2 (m, 4H, ArH ring A), 6·9 (s, 1H) and 6·8 (s, 1H; *p*-ArH ring D), 6·0 (s, 2H, O·CH_2·O), 4·5 (t, 1H, *J* 2 Hz, C*H*·OH), 4·0 (d, 1H, *J* 15 Hz) and 3·8 (d, 1H, *J* 15 Hz, ArCH_2·N), 3·7—2·9 (m, 5H, aliphatic H), and 3·85br p.p.m. (d, 1H, CH·O*H*); *m/e* 295 (75%), 278 (70%), 190 (10%), and 104 (100%).

2,3-Dimethoxyberbine (2e).—(a) A solution of 2,3-dimethoxy-5-hydroxyberbine hydrochloride (100 mg) in 6N-aqueous HCl (10 ml) was hydrogenated over 10% palladium on charcoal (30 mg) at room temperature and atmospheric pressure. After 2 h, the catalyst was filtered off and the filtrate was evaporated under reduced pressure.

Trituration of the residue with acetone produced a white solid which was recrystallised from ethanol–ethyl acetate (32 mg, 35%), m.p. 236—238°. (A mixed m.p. with an authentic specimen of 2,3-dimethoxyberbine hydrochloride caused no depression.)

(b) A suspension of the lactam (8) (100 mg) in tetrahydrofuran (10 ml) was treated with lithium aluminium hydride (200 mg) portionwise during 15 min. The mixture was then heated to reflux and maintained at this temperature in an atmosphere of N_2 for 4 h. Excess of hydride was destroyed with 30% sodium potassium tartrate solution; the supernatant liquid was decanted, diluted with water (10 ml), and evaporated. Ethanol (5 ml) and then sodium borohydride (200 mg) were added, and the solution was warmed on a steam-bath for 1 h. Evaporation of the solvent and extraction with ether afforded 2,3-dimethoxyberbine (60 mg, 62%), m.p. 142° (undepressed mixed m.p. and superimposable i.r. spectra with an authentic sample).

[1/615 *Received, April 26th,* 1971]

ASPECTS OF ISOCOUMARIN CHEMISTRY

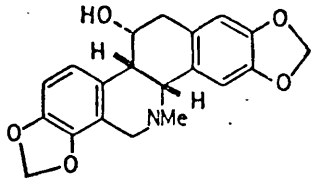
(J.Chem.Soc.C., 1971, 3935)

Aspects of Isocoumarin Chemistry. Part II.†

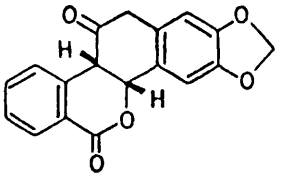
By S. F. Dyke, M. Sainsbury, and B. J. Moon, School of Chemistry and Chemical Engineering, University of Bath, Somerset

In some model experiments aimed at the synthesis of chelidonine, 4b,10b-dihydro-2,3-methylenedioxy-6*H*-benzo-[*d*]naphtho[1,2-*b*]pyran-6,11(12*H*)-dione (2) has been synthesised from homophthalic acid, but attempts to replace the heterocyclic oxygen atom by a nitrogen atom have failed.

DESPITE much effort,[1] the alkaloid chelidonine (1) has has not yet been synthesised. It is well known [2] that isocoumarins may be converted into isocarbostyrils, and although the corresponding reaction with dihydroisocoumarins is uncommon,[3] we hoped that it would be possible to synthesise chelidonine by this type of approach. To test the feasibility of the route, we have synthesised the model compound (2), but our attempts to replace the heterocyclic oxygen atom by a nitrogen atom have failed.



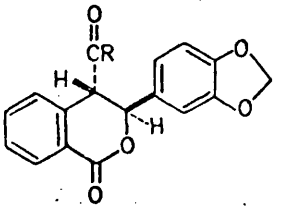
(1)



(2)

The known [4] dihydroisocoumarin (3; R = OH) was obtained by the condensation of homophthalic anhydride with piperonal (3,4-methylenedioxybenzaldehyde). No comment about stereochemistry was made initially,[4] but since, in the n.m.r. spectrum, the value of $J_{3,4}$ was 7 Hz, we have allotted the *trans* geometry to this compound. When the diazo-ketone [4] (3; R = CHN_2) was treated with hydrochloric acid it was converted into the *cis*-chloro-ketone (4) ($J_{3,4}$ 4 Hz), which, with tin(IV) chloride in chloroform, was converted into the *cis*-dihydroisocoumarin (2). However, if dichloromethane, rather than chloroform, was used as solvent, the chloro-compound (5) resulted, which, when warmed briefly with dimethyl sulphoxide, was converted into the olefin (6).

Attempts to replace the heterocyclic oxygen atom of compound (2) with a nitrogen atom were unsuccessful: treatment with ammonia under pressure gave only the phenylnaphthalene (7; R = H), and treatment with ethanolic ammonia afforded the corresponding acid (7; R = CO_2H). Several attempts were made to dehydrogenate compound (2) to the corresponding isocoumarin, but without success, and efforts to introduce nitrogen at an earlier stage in the synthesis also failed. For example when the chloro-ketone (4) was treated with manganese dioxide, the product was the methyl ketone (8), and dehydrogenation of the dihydroisocoumarin (3; R = OH) gave the known [4,5] *trans*-acid (9), and not the required isocoumarin.



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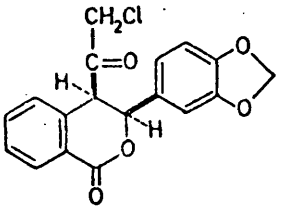

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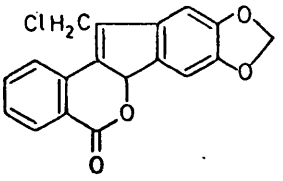

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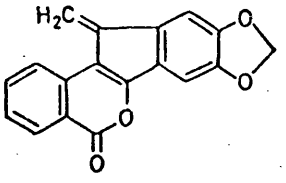

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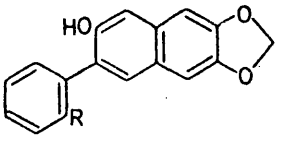

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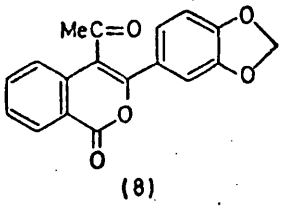

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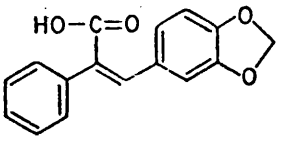

(9)

EXPERIMENTAL

U.v. spectra were recorded for ethanolic solutions, unless otherwise stated. I.r. data refer to Nujol mulls. N.m.r. spectra were recorded with a Varian A60 spectrometer (tetramethylsilane as internal standard).

4-Chloroacetyl-3,4-dihydro-3-(3,4-methylenedioxyphenyl)-isocoumarin (4).—The diazo-ketone [4] (3; R = CHN_2) (3·5 g) was dissolved in pure chloroform (120 ml) and hydrogen chloride was bubbled through the solution for 30 min. The chloroform was evaporated off to leave a solid which afforded the *chloro-ketone* (4) (3·4 g, 93%) as

† Part I, D. W. Brown, S. F. Dyke, M. Sainsbury, and G. Hardy, *J. Chem. Soc.* (*C*), 1971, 3219.

[1] See S. F. Dyke, M. Sainsbury, D. W. Brown, M. N. Palfreyman, and E. P. Tiley, *Tetrahedron*, 1968, **24**, 6703 and references cited therein.

[2] R. D. Barry, *Chem. Rev.*, 1964, **64**, 229.

[3] P. Maittre, *Colloq. internat. Centre nat. Rech. sci.* (*Paris*), 1955, No. 64, 197 (*Chem. Abs.*, 1961, **55**, 10,426).

[4] J. B. Jones and A. R. Pinder, *J. Chem. Soc.*, 1958, 2612.

[5] H. J. E. Loewenthal and R. Pappo, *J. Chem. Soc.*, 1952, 4799.

feathery needles, m.p. 164—165° (from ethanol) (Found: C, 63·0; H, 4·0; Cl, 10·3. $C_{18}H_{13}ClO_5$ requires C, 62·7; H, 3·8; Cl, 10·0%), $\nu_{max.}$ 1720 cm^{-1} (CO·O and CO·CH_2Cl), $\lambda_{max.}$ 205 (ε 43,000), 236 (13,800), and 288 nm (6300), $\lambda_{min.}$ 226 (ε 12,200) and 267 nm (2800), δ [$(CD_3)_2SO$] 4·86 (2H, s, CH_2Cl), 5·01 (1H, d, *J* 4 Hz, 3- or 4-H), 6·00 (2H, s, CH_2O_2), 6·11 (1H, d, *J* 4 Hz, 4- or 3-H), 6·9 (3H, m, aromatic), and 7·8 p.p.m. (4H, m, 5-, 6-, 7-, and 8-H).

4b,10b-*Dihydro*-2,3-*methylenedioxy*-6H-*benzo*[d]*naphtho*-[1,2-b]*pyran*-6,11(12H)-*dione* (2).—The 4-chloroacetyl-3,4-dihydroisocoumarin (4) (1·0 g) was dissolved in pure chloroform (100 ml) and treated dropwise with tin(IV) chloride (0·3 ml) at 0°. This solution was stirred for 2 h and then kept at 0° overnight. After decomposition of the precipitated complex with 6N-hydrochloric acid, the chloroform layer was separated, washed with very dilute sodium hydroxide solution, and water, dried ($MgSO_4$), and evaporated. This gave a pale yellow oil which was triturated with petroleum (b.p. 30—40°) to give a solid. Recrystallisation from benzene gave the *benzonaphthopyran* (2) (0·55 g, 62%) as rods, m.p. 202—203° (Found: C, 70·0; H, 4·0. $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%), $\nu_{max.}$ 1730 (CO·O) and 1715 cm^{-1} (CO), $\lambda_{max.}$ 205 (ε 42,900), 236 (11,700), and 289 nm (5300), $\lambda_{min.}$ 226 (ε 10,000) and 266 nm (2100), δ [$(CD_3)_2SO$] 3·47 and 4·58 (2H, q, *J* 17 Hz, CH_2·CO), 4·86 (1H, d, *J* 4 Hz, 4b- or 10b-H), 6·00 (1H, d, *J* 4 Hz, 10b- or 4b-H), 6·08 (2H, s, CH_2O_2), 7·00 (2H, s, 1- and 4-H), 7·6 (3H, m, 8-, 9-, and 10-H), and 8·1 p.p.m. (1H, m, 7-H).

11-*Chloromethyl*-2,3-*methylenedioxy*-4bH,6H-*benz*[d]*indeno*-[1,2-b]*pyran*-6-*one* (5).—The 4-chloroacetyl-3,4-dihydroisocoumarin (4) (200 mg) was dissolved in dry dichloromethane (20 ml) and treated dropwise with tin(IV) chloride (0·1 ml) at 0°. This solution was stirred for 1 h, then kept at 0° overnight. After decomposition of the oily complex with 6N-hydrochloric acid, the chloroform layer was separated, washed with sodium carbonate solution and water, dried ($MgSO_4$), and evaporated. This gave a yellow solid which afforded the benzindenopyran (5) (150 mg, 79%) as yellow needles, m.p. 174—175° (decomp.; remelts 230—232°) (from benzene), *m/e* 326 (M^+) and 290 (Found: C, 66·2; H, 3·4; Cl, 10·6. $C_{18}H_{11}ClO_4$ requires C, 66·2; H, 3·4; Cl, 10·8%), $\nu_{max.}$ 1720 (CO·O) and 1605 cm^{-1} (C=C), $\lambda_{max.}$ 205 (ε 29,000), 237 (16,900), and 376 nm (5600), $\lambda_{min.}$ 227 (ε 15,500) and 341 nm (5100), $\lambda_{infl.}$ 252 nm (ε 9600), δ (CF_3·CO_2H) 4·63 (2H, s, CH_2Cl), 5·95 (1H, s, 4b-H), 6·03 (2H, s, CH_2O_2), 7·08 (1H, s, 1- or 4-H), 7·15 (1H, s, 4- or 1-H), 7·80 (3H, m, 8-, 9-, and 10-H), and 8·25 p.p.m. (1H, d, 7-H).

11-*Methylene*-2,3-*methylenedioxy*-6H-11H-*benz*[d]*indeno*-[1,2-b]*pyran*-6-*one* (6).—The 11-chloromethylbenzindenopyran (5) (50 mg) was boiled with dimethyl sulphoxide (2 ml) for 5 min. Chloroform was added to the cooled solution, and the precipitate yielded orange needles of the 11-*methylene derivative* (6) (20 mg), m.p. 232—233° (from chloroform), M^+ 290 (Found: C, 74·3; H, 3·2. $C_{18}H_{10}O_4$ requires C, 74·5; H, 3·5%), $\nu_{max.}$ 1725 (CO·O), 1615 (C=CH_2), 1550 (C=C), and 880 cm^{-1} (C=CH_2), $\lambda_{max.}$ 214 (ε 27,100), 236 (27,900), 249 (27,900), 292 (30,200), and 376 nm (13,200), $\lambda_{min.}$ 224 (ε 23,600), 243 (27,500), 272 (16,300), and 328 nm (6200), δ (100 MHz; $CDCl_3$) 5·95 (2H, s, CH_2O_2), 6·02 (1H, s) and 6·18 (1H, s) (>C=CH_2), 6·93 (1H, s, 1- or 4-H), 7·60 (3H, m, 8-, 9-, and 10-H), and 8·26 p.p.m. (1H, d, *J* 8 Hz 7-H).

Reactions of the Benzonaphthopyran (2).—(a) *With liquid ammonia.* The benzonaphthopyran (2) (100 mg) dissolved in liquid ammonia (50 ml) in a stainless steel vessel was shaken at 160° and 120 atm for 24 h. Evaporation of the ammonia afforded a brown solid which was chromatographed over silica. Recrystallisation of the product from ethanol gave 6,7-*methylenedioxy*-3-*phenyl*-2-*naphthol* (7; R = H) (10 mg) as needles, m.p. 192—193°, M^+ 264, $\nu_{max.}$ 1600 (aromatics) and 3380 cm^{-1} (OH) (Found: C, 77·4; H, 4·6. $C_{17}H_{12}O_3$ requires C, 77·3; H, 4·6%).

(b) *With ethanolic ammonia.* The benzonaphthopyran (2) (200 mg) was heated under reflux with ethanol (25 ml) and ammonia (*d* 0·880; 5 ml) for 4 h; more ammonia was added every h. The solution was evaporated under reduced pressure and the solid produced was dissolved in water. Acidification of the solution gave a precipitate which afforded 3-(2-carboxyphenyl)-6,7-methylenedioxy-2-naphthol (7; R = CO_2H) (150 mg) as an orange amorphous solid, m.p. 140—141° (decomp.) (from aqueous acetic acid), M^+ 308, $\nu_{max.}$ 1690 (CO_2H) and 3430 cm^{-1} (OH).

This phenolic acid was heated in quinoline (5 ml) for 15 min at 150°. After the evolution of carbon dioxide, the mixture was cooled and chloroform was added. The solution was extracted with 6N-hydrochloric acid; the chloroform layer was washed with water, dried ($MgSO_4$), and evaporated to leave a solid which was chromatographed on silica. Recrystallisation of the product from ethanol gave 6,7-methylenedioxy-3-phenyl-2-naphthol (7; R = H) as needles, m.p. 192—193°, identical with the product from the liquid ammonia reaction.

4-*Acetyl*-3-(3,4-*methylenedioxyphenyl*)*isocoumarin* (8).—The 4-chloroacetyl-3,4-dihydroisocoumarin (4) (200 mg) was heated under reflux with active manganese dioxide (1·0 g) in benzene (50 ml) for 4 h. After filtration the solution was evaporated to leave a yellow oil, which solidified on trituration with petroleum (b.p. 30—40°). Recrystallisation from ethanol gave the 4-*acetylisocoumarin* (8) (35 mg) as yellow cubes, m.p. 184—185°, M^+ 308 (Found: C, 70·2; H, 4·1. $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%), $\nu_{max.}$ 1723 (CO·O), 1700 (CO), and 1613 cm^{-1} (C=C), $\lambda_{max.}$ 205 (ε 30,800), and 370 nm (14,700), $\lambda_{min.}$ 292 nm (ε 4400), $\lambda_{infl.}$ 234 nm (ε 13,900).

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THE SYNTHESIS OF 5-HYDROXYBERBINE DERIVATIVES

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THE SYNTHESIS OF 5-HYDROXYBERBINE DERIVATIVES[1]

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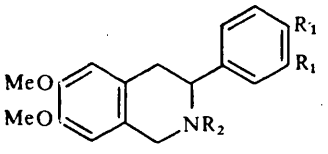
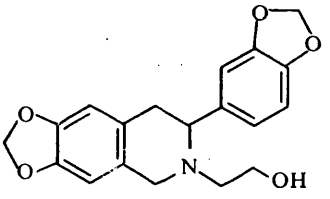
Abstract—The syntheses of 5-hydroxy-2,3,10,11-tetramethoxyberbine (**4**, R_1 = OMe; R_2 = OH) and 5-hydroxy-2,3-methylenedioxy-10,11-dimethoxyberbine (**4**, $R_1 + R_1 = CH_2O_2$; R_2 = OH) are described. The structures have been established by chemical and spectral methods and, in the former case, the relative stereochemistry has been elucidated. These are the first examples of 5-hydroxyberbine derivatives to be prepared.

RECENTLY[2] we described syntheses of tetrahydroberbering and tetrahydropalmatine based upon the cyclization of 2-β-arylethyl-1,2-dihydroisoquinolines, the route pioneered by Battersby *et al.*[3] This method together with the route developed by Bradsher *et al.*,[4] are now the ones of choice for syntheses[5] of berbine derivatives, especially those possessing the 2,3,9,10-tetra-oxygenation pattern. Another potential route to the berbine nucleus involves the addition of a two-carbon unit to a 3-aryl-1,2,3,4-tetrahydroisoquinoline (**1**).



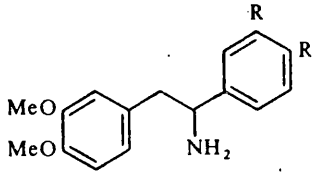
1



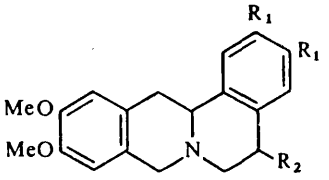
2

A previous attempt to cyclize the amino-alcohol (**2**) was unsuccessful,[6] but it seemed to us that cyclization of the corresponding aldehyde, or its dialkyl acetal should be feasible. Accordingly, a synthesis of (±)-norcoralydine was attempted from **1** (R_1 = OMe; R_2 = H).

Considerable improvements have been made (Experimental)[7] in the preparation of the known[7,8] amine **3** (R = OMe), which, when treated with HCHO/HCl under the conditions of the Pictet–Spengler reaction,[10] gave the required isoquinoline derivative **1** (R_1 = OMe; R_2 = H). The latter compound failed to react with chloracetal, in keeping with previous experience.[11,12] A convenient synthesis of substituted amino-acetaldehyde dialkyl acetals, originally devised by Frank and Purves,[13] and subsequently used by Bobbitt *et al.*[12] and by us,[2] was successful. The amine **1** (R_1 = OMe; R_2 = H) was reacted with glycidol to give the glycol **1** (R_1 = OMe; R_2 = —$CH_2CHOHCH_2OH$) which, without isolation, was oxidized with sodium periodate. Purification of **1** (R_1 = OMe; R_2 = —CH_2CHO) was achieved by

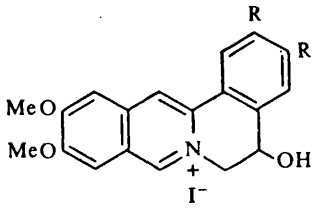


3

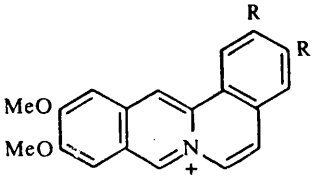


4

column chromatography, and the product, a yellow glass (IR band at 1730 cm^{-1}), was dissolved in 6N HCl, and the solution was left at room temperature overnight. A 70% yield of a base hydrochloride, $C_{21}H_{25}NO_5.HCl$ was obtained. The IR spectrum, which is devoid of absorption in the region 1800–1600 cm^{-1}, exhibits a strong band at 3300 cm^{-1}, which is shifted to 3500 cm^{-1} in the free base. The appearance of Bohlmann bands at 2760 cm^{-1} in the IR spectrum of the base indicated that the product is a berbine derivative with *trans*-fusion of the two central rings. The NMR spectrum of the base contains resonances associated with only 4 aromatic protons, 4 methoxyl groups, and a total of 9 aliphatic protons—reducing to 8 on deuteration. This evidence is compatible with structure **4** (R_1 = OMe; R_2 = OH) for the cyclization product. Dehydrogenation of this material with iodine afforded, in

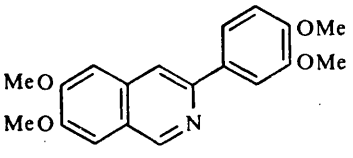


5



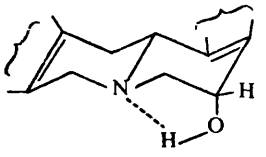
6

88% yield, a quaternary salt, the NMR spectrum of which is diagnostic for **5** (R = OMe). Brief treatment with 2N HCl caused dehydration of this salt to yield the known[14] iodide **6** (R = OMe). Reduction of **6** (R = OMe) with $NaBH_4$ gave norcoralydine **4** (R_1 = OMe; R_2 = H), identical with an authentic[15] specimen. The overall yield of norcoralydine from the 3-aryltetrahydroisoquinoline **1** (R_1 = OMe; R_2 = H) was 40%, and of the 5-hydroxyberbine **4** (R_1 = OMe; R_2 = OH), 63%. Recently[16] norcoralydine has been obtained, in 22·5% yield, by quaternization of **7** with bromoacetaldehyde, followed by cyclization to **6** (R = OMe) and catalytic hydrogenation.

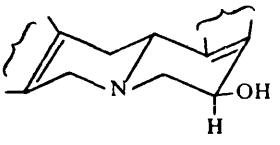


7

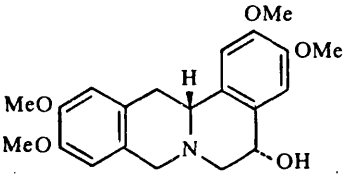
Fractional crystallization of the original cyclization product **4** (R_1 = OMe; R_2 = OH), eventually gave one pure diastereomorph, but it was not possible to isolate a second pure base. However, when the original mixture of diastereomorphs was treated with acetic anhydride, a separable mixture of two O-acetates resulted, O-*acetate A*, m.p. 188–189° (51% of the mixture) and O-*acetate B*, m.p. 162–163° (36%). Each O-acetate was then separately reduced with LAH to afford the hydroxy base A, m.p. 194–195° (identical with that obtained by fractional crystallization of the original basic product), and base B, m.p. 175–177°. The IR spectra of both O-acetates, and both bases exhibit the characteristic Bohlmann bands at *ca* 2800 cm^{-1}, and these compounds therefore exist in the *trans*-quinolizidine configuration. The IR spectrum of O-*acetate A* exhibits a band at 1715 cm^{-1} for the acetate carbonyl group, which is indicative of some interaction with the unshaired electron pair on the N atom. The OH band in the derived base A is a broad absorption in the region 3550–3450 cm^{-1}. In contrast, O-*acetate B* exhibits a CO frequency at 1735 cm^{-1}, typical of an acetate function, and the OH group of base B absorbs as a sharp band at 3540 cm^{-1}. An inspection of Dreiding models indicates that intramolecular H-bonding to the N atom can occur if the OH group of base A is axial (**8a**). The properties of base B are consistent with it possessing an equatorial OH group (**9a**). The NMR spectra of the O-acetates confirm these stereochemical assignments. The Me protons of the acetyl function in O-*acetate A*, because of the interaction with the N atom, resonate at higher field (2·10 δ) than the corresponding protons in O-*acetate B* (2·16 δ). The relative configurations of the two bases are then as depicted in **8b** and **9b**, respectively.



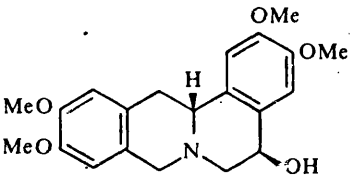
8a



9a

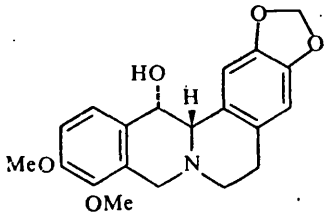


8b

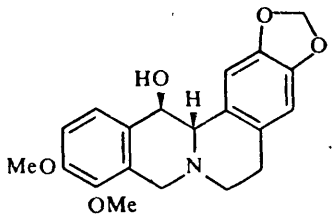


9b

An analogous situation exists in the 13-hydroxytetrahydroprotoberberines, where the OH group is also β to the N atom. Thus, the IR spectra of ophiocarpine **10a** and 13-epiophiocarpine **10b** show similar differences in the OH region.

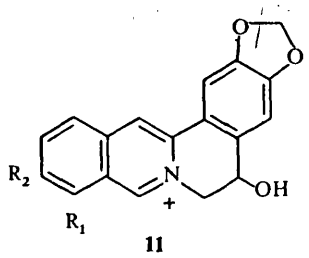


10a



10b

The reactions described above, which constitute the first synthesis of a 5-hydroxyberbine derivative, are significant in the light of the recent isolation of two alkaloids bearing this structural feature. Berberastine **11** ($R_1 = R_2 = OMe$) is a minor alkaloid of *Hydrastis canadensis*, and was first characterized by Nijland.[18] Thalidastine

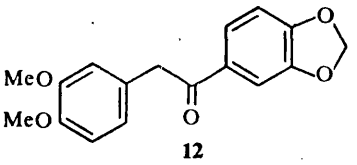


11

11 ($R_1 = OMe$; $R_2 = OH$), however, is one of the major alkaloids of *Thalictrum fendleri*; its structure was deduced[19] from the NMR spectrum of deoxythalidastine and from the mass spectrum of tetrahydrothalidastine. Deoxythalidastine has been synthesized.[20]

The mass spectrum of **4** ($R_1 = OMe$; $R_2 = OH$) shows marked differences in the relative abundances of the various fragment ion peaks from those reported[19] for tetrahydrothalidastine. Thus, the base peak of the spectrum of **4** ($R_1 = OMe$; $R_2 = OH$) at *m/e* 164 corresponds (Chart I) to ion (e) and is derived from the characteristic retro-Diels-Alder cleavage of ring C. This is typical of 10,11-dimethoxy-substituted berbines. The ion **d** is of very low abundance, in contrast to the spectrum of tetrahydrothalidastine in which the analogous ion is the base peak. This difference, which has been observed in the spectra of other tetrahydroprotoberberines,[21] and is associated with the presence of a phenolic OH group in ring D, may prove useful for distinguishing between differently substituted 5-hydroxyberbine derivatives.

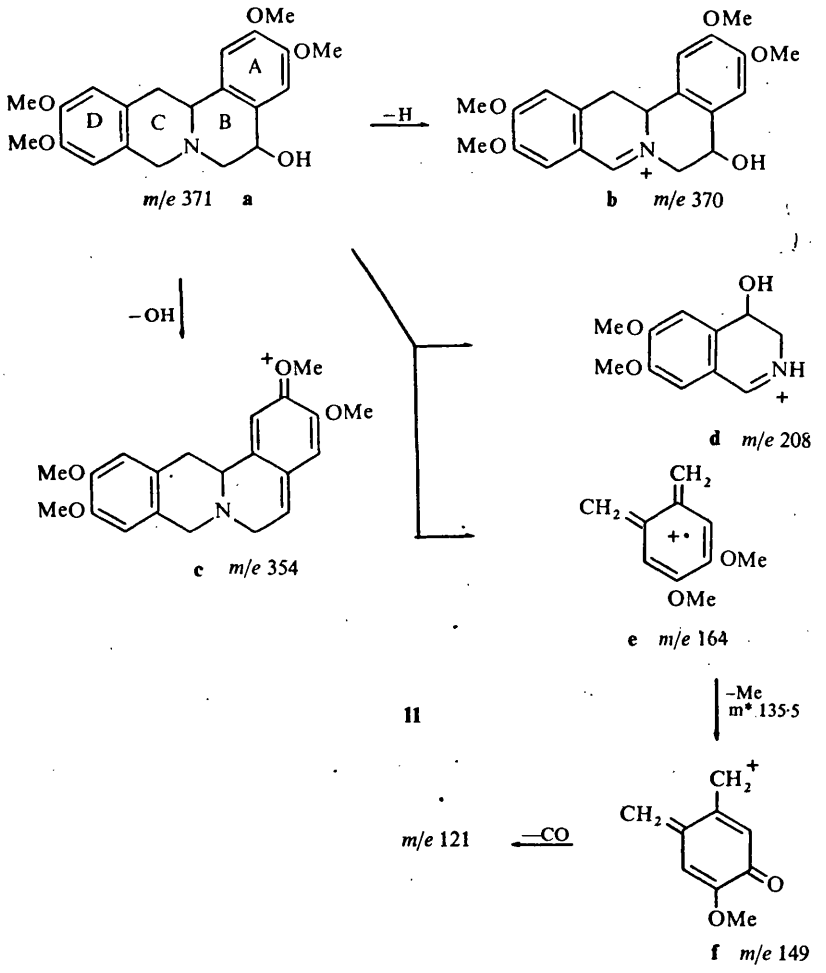
Since it is possible that a methylenedioxy group may be cleaved under the acid conditions that led to **4** ($R_1 = OMe$; $R_2 = OH$), we decided, before embarking upon a synthesis of berberastine, to repeat the sequence using the 3-aryl-1,2,3,4-tetrahydroisoquinoline **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) in place of **1** ($R_1 = OMe$; $R_2 = H$). The required benzyl ketone (**12**) was obtained, in 60% yield, by a Friedel–Crafts reaction between homoveratryl chloride and methylenedioxybenzene in the presence of $SnCl_4$ at $-10°$. Above this temperature cleavage of the methylenedioxy group occurred. The conversion of **12** to **3** ($R + R = CH_2O_2$) and thence to



12

1 ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) was conducted as for **1** (R_1 = OMe; $R_2 = H$), and further elaboration to **4** ($R_1 + R_1 = CH_2O_2$; R_2 = OH) was achieved in 48% yield based upon the tetrahydroisoquinoline derivative **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$). This time no attempt was made to separate the diastereomorphs of **4** ($R_1 + R_1 = CH_2O_2$; R_2 = OH); dehydrogenation gave **5** ($R + R = CH_2O_2$) in almost quantitative yield, and dehydration gave the known[14] benz[a]acridizinium ion **6** ($R + R = CH_2O_2$). Reduction of the latter with $NaBH_4$ provided tetrahydropseudoberberine[22] **4** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$). The overall yield of tetrahydropseudoberberine from **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) was 32%.

CHART 1



EXPERIMENTAL

IR spectra were recorded for nujol mulls unless otherwise stated, in the case of solids, or for thin films in the case of liquids, using a Perkin–Elmer 237 spectrophotometer. UV spectra were recorded for solns in EtOH, unless otherwise stated, using a Perkin–Elmer 137 spectrophotometer. NMR spectra were determined using a Varian A60 spectrometer where absorptions are assigned to hydroxylic protons the assignments are confirmed by deuteration experiments. Mass spectra (70 eV) were obtained using an A.E.I. MS12 spectrometer. M.ps are uncorrected.

3,4-*Dimethoxyphenylacetyl chloride.* Thionyl chloride (38·0 g) was added to a soln of 3,4-dimethoxyphenylacetic acid (42·0 g) in dry benzene (500 ml) at 30° and the whole was allowed to stand for ¾ hr, then heated under reflux for 1½ hr. The solvent and excess $SOCl_2$ were evaporated under reduced pressure and the acid chloride distilled *rapidly* as a clear liquid (41·0 g). Bath temp 220°/0·13 torr ν_{max}. 1785 cm^{-1}.

3,4-*Dimethoxybenzyl*-3,4-*dimethoxyphenyl ketone.* Anhyd $AlCl_3$ (37 g) was added to a soln of 1,2-dimethoxybenzene (30·5 g) and 3,4-dimethoxyphenylacetyl chloride in CH_2Cl_2 (150 ml), and the mixture heated under reflux for 1¾ hr. The cooled soln was poured into a stirred mixture of water (70 ml), 12N HCl (150 ml), and ice (200 g). The organic phase was separated and the aqueous phase extracted (3 × 100 ml CH_2Cl_2). The combined extracts were dried and the solvent evaporated to yield an oil which solidified on cooling. Crystallization from aqueous EtOH gave the ketone as a white solid 25·0 g) m.p. 105–107° (Lit.[11] 103·5–104·5°).

3,4-*Dimethoxybenzyl*-3,4-*methylenedioxyphenyl ketone.* To a stirred mixture of methylenedioxybenzene (7·3 g) and $SnCl_4$ (18·4 g) in CH_2Cl_2 (50 ml) at −10°, was added a soln of homoveratryl chloride (13·0 g) in dry CH_2Cl_2 (50 ml). The mixture was allowed to attain room temp and stirred for a further 2 hr, then poured into 6N HCl (100 ml), and stirred for 16 hr. The product was worked up as the previous compound giving the *ketone* (10·8 g), m.p. 110–111° as cream prisms from EtOH. (Found: C, 68·1; H, 5·5. $C_{17}H_{16}O_5$ requires: C, 68·0; H, 5·3%).

Bis-1,2-(3,4-*dimethoxyphenyl*) *ethylamine* (3, R = OMe). A mixture of 3,4-Dimethoxybenzyl-3,4-dimethoxyphenyl ketone (25·0 g) ammonium formate (50·0 g), 98–100% formic acid (15 ml), and fermamide (15 ml) was heated at 185° for 3½ hr under N_2. The mixture at 60° was poured with stirring into ice cold water (100 ml) and the solid collected after 10 min. The solid was suspended in 5N H_2SO_4 (250 ml) and the mixture heated under reflux for 2½ hr. The resulting soln was cooled, extracted (1 × 50 ml CH_2Cl_2), and to the stirred aqueous phase was added charcoal (2·5 g). After filtration the soln was basified with 30% NaOH aq cooled to 10° and the base collected. This was washed with water and dried at 60° in a vacuum oven to give the amine as a white solid, (20·2 g) m.p. 106–107° (Lit.[8] 107°).

1-(3,4-*Methylenedioxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-*ethylamine* (3, R = CH_2O_2), was prepared as the previous compound and obtained as a sticky brown solid (70%); characterized as the *amine hydrochloride*, m.p. 225–226°, which separated from EtOH as colourless prisms. (Found: C, 60·5; H, 6·1; Cl, 10·7; N, 4·0. $C_{17}H_{20}NO_4Cl$ requires: C, 60·45; H, 5·9; Cl, 10·5; N, 4·15%).

3-(3,4-*Dimethoxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (I, R_1 = OMe, R_2 = H). The appropriate ethylamine (5·0 g) and 18% aqueous formaldehyde (12 ml) were heated together on a steam bath for ⅔ hr. 3N HCl (8·0 ml) was added and the mixture heated for a further ½ hr. On cooling the amine hydrochloride separated as white crystals (4·8 g), m.p. 278–280°, from which the free base was obtained m.p. 97–98° (EtOH). The methiodide was prepared in ether, m.p. 250° (EtOH). (Lit.[8] 250–252°).

3-(3,4-*Methylenedioxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (I, R_1R_1 = CH_2O_2, R_2 = H) was prepared similarly giving the crude base (4·5 g) m.p. 105–110° which was characterized as the *amine hydrochloride*, m.p. 261–263°, obtained as white prisms from EtOH. (Found: C, 61·5; H, 5·8; Cl, 10·4; N, 4·2. $C_{18}H_{20}NO_4Cl$ requires: C, 61·8; H, 5·7; Cl, 10·2; N, 4·0%).

2,3,10,11-*Tetramethoxy*-5-*hydroxyberbine* (4, R_1 = OMe, R_2 = OH). The isoquinoline 1 (R_1 = OMe, R_2 = H), (3·3 g), and glycidol (0·9 g) were heated together on a steam bath for 2 hr. The product was treated with chloroform (15 ml), and water (15 ml) and to the well stirred mixture at 0° was added dropwise sodium metaperiodate (2·2 g) in water (15 ml). After the addition the mixture was brought to pH8 using 1N NaOH and the whole stirred for 3 hr. The organic phase was separated, dried, and evaporated to give a yellow glass (ν_{max} cm^{-1} 1730) which did not crystallize. This product was purified by column chromatography using alumina packing and benzene:chloroform (1:1) as eluant, giving the *amino-aldehyde* (1, R_1 = OMe, R_2 = CH_2CHO) (3·35 g). This compound (3·3 g) was dissolved in 6N HCl (50 ml) and allowed to stand at room temp for 18 hr during which time the *hydrochloride of* 4 (R_1 = OMe, R_2 = OH) (2·52 g), m.p. 228–229° (EtOH) separated as white needles; ν_{max} cm^{-1} 3300 (OH), 2520 ($\overset{+}{N}H$). (Found: C, 61·5; H, 6·6; Cl, 8·7; N, 3·6. $C_{21}H_{26}NClO_5$ requires: C, 61·8; H, 6·4; Cl, 8·7; N, 3·4%). The *amine* (4, R_1 = OMe, R_2 = OH) was

obtained from its salt as white needles m.p. 194–195° after several recrystallizations (EtOH) λ_{max} (ε) nm. 227 sh (22.250). 284 (7770). ν_{max} cm^{-1}. 3500. 2760. 1610; NMR ($CDCl_3$); 2·5–4·0 (7H. m); 3·7 (1H. broad s. OH); 3·75–3·8 (12H. MeO groups); 4·45 (1H. m. CHOH); 6·5. 6·6. 6·75. 6·85 (each 1H. aromatic H's). *m/e* (Rel. int.) 371 (20). 354 (9). 165 (25). 164 (100). 149 (7). 121 (9). 47 (8). 46 (28). 45 (57). 44 (98). (Found: C. 67·6; H. 7·0; N. 3·9. $C_{21}H_{25}NO_5$ requires: C. 67·9; H. 6·8; N. 3·8%). The methiodide of **4** (R_1 = OMe. R_2 = OH) was prepared in acetone and obtained as cream coloured prisms m.p. 241–242° (EtOH); ν_{max} cm^{-1}. 3320. (Found: C. 51·3; H. 5·7; N. 2·8; I. 24·8. $C_{22}H_{28}NO_5I$ requires: C. 51·5; H. 5·5; N. 2·7; I. 24·7%).

2.3-*Methylenedioxy*-5-*hydroxy*-10.11-*dimethoxyberbine* (**4**. R_1R_1 = CH_2O_2. R_2 = OH) was prepared in the same way as its tetramethoxy-analogue. The *amino-aldehyde* **1** (R_1R_1 = CH_2O_2. R_2 = CH_2CHO) was obtained as a glass in 67% yield from **1** (R_1R_1 = CH_2O_2. R_2 = H). The *hydrochloride of* **4** (R_1R_1 = CH_2O_2. R_2 = OH) separated from the mixture as cream coloured needles (72%). m.p. 188–190°. ν_{max} cm^{-1}. 3430 (OH), 3290, (OH), 2660–2600 ($\overset{+}{N}H$). (Found: C, 60·4; H, 6·2; N, 3·8. $C_{20}H_{22}NO_5Cl.H_2O$ requires: C, 60·3; H, 6·4; N, 3·3%). The *amine* **4** (R_1R_1 = CH_2O_2; R_2 = OH) was obtained as pale yellow needles (EtOH, charcoal) m.p. 105–106° λ_{max}(ε) nm, 230 sh (20,800), 289 (7900), ν_{max} cm^{-1}, 3450–3350 (OH), 2790, 1610, *m/e* (Rel. int.), 355 (20), 338 (11), 165 (26), 164 (100), 149 (10), 121 (10), 63 (7), 46 (98), 45 (97), 44 (48). (Found: C, 66·7; H, 6·5: N, 3·7. $C_{20}H_{21}NO_5$ $\frac{1}{2}$ C_2H_5OH requires: C, 66·7; H, 6·4; N, 3·7%).

Dehydrogenation and dehydration of the 5-*hydroxy berbines* 2.3.10.11-*tetramethoxy*-5-*hydroxyberberinium iodide* (**5**. R = OMe). The berbine **4** (R_1 = OMe. R_2 = OH). (0·85 g). dissolved in EtOH (25 ml) was heated under reflux with AcOK (1·0 g) while a soln of I_2 (1·25 g) in EtOH (60 ml) was added over $\frac{1}{4}$ hr. The mixture was heated for a further $\frac{1}{2}$ hr after which time the periodide was collected. suspended in water and SO_2 passed through the suspension for $\frac{1}{2}$ hr. The berberinium iodide **5** (R = OMe_3), (0·99 g), m.p. 265–267°, was collected and recrystallized (water) giving yellow needles m.p. 243–245°. λ_{max} (ε) nm (90% aqueous EtOH). 240 sh (16.000). 265 (11.800). 291 (25.200). 311 sh (16.800). 340 (6700); ν_{max} cm^{-1}. 3530 (OH). 3400–3300 (OH). 1635. 1615. 1575; NMR (DMSO.d_6); 3·8–4·1 (12H. MeO groups); 4·85 (2H. d. J = 5·5 Hz. CH_2 CH.OH); 5·1 (1H. broad. OH); 5·85 (1H. t. J = 5·5 Hz. CH_2CH.OH); 7·15 (1H. s. 4-H); 7·7 (3H. broad s. 1-H. 9-H and 12-H); 8·95 (1H. s. 13-H); 9·7 (1H. s. 8-H). (Found: C. 50·0; H. 4·7; N. 3·0. $C_{21}H_{22}NO_5I$. $\frac{1}{2}$ H_2O requires: C. 50·0; H. 4·55; N. 2·8%).

2.3-*Methylenedioxy*-5-*hydroxy*-10.11-*dimethoxyberberinium iodide* (**5**. RR = CH_2O_2) was prepared from the berbine **4** (R_1R_1 = CH_2O_2. R_2 = OH) by the above method and obtained as yellow needles (92%) m.p. 220–222° (water); λ_{max} (ε) nm. 267 (26.700). 289 (33.900). 314 (19.600). 341 (9200); ν_{max} cm^{-1}. 3340. 1630. 1610. 1570; NMR (DMSO d_6); 4·05 and 4·15 (each 3H, s, OMe); 4·75–5·1 (2H. m. CH_2CH.OH); 5·6 (1H, broad, OH); 5·95 (1H. broad t. CH_2CH.OH); 6·2 (2H. s. CH_2O_2); 7·15 (1H. s. H-4); 7·75 (3H. broad s. 1-H. 9-H and 12-H); 8·85 (1H. s. 13-H); 9·4 (1H. s. 8-H). (Found: C. 50·2; H. 3·55; N. 3·2. $C_{20}H_{18}NO_5I$ requires: C. 50·1; H. 3·75; N. 2·9%).

2.3.10.11-*Tetramethoxybenz*[a] *acridizinium chloride* (**6**. R = OMe). The iodide **5** (R = OMe). (0·36 g) in 2N HCl (120 ml) was heated under reflux for $\frac{1}{4}$ hr. on cooling the product was collected and recrystallized (aqueous MeOH) giving yellow crystals (0·25 g) m.p. 242–244° dec. (sealed tube) (Lit.[14] m.p. 240–242°); λ_{max} (ε) nm (90% aqueous ethanol). 278 (18.300). 309 (23.100). 322 (15.400), 417 (2900) see Ref. 14; NMR (DMSO.d_6); 3·9. 3·93. 3·95. 4·0 (each 3H. s. OMe); 7·1 (4H. broad s. 1-H. 4-H. 9-H and 10-H); 7·5 (1H. d. J = 7·5 Hz. 5-H); 7·65 (1H. d. J = 7·5 Hz. 6-H); 8·8 (1H. s. 13-H); 9·5 (1H. s. 8-H).

2.3-*Methylenedioxy*-10.11-*dimethoxybenz*[a] *acridizinium chloride* (**6**. RR = CH_2O_2) was prepared from **5** (RR = CH_2O_2) by the above method and obtained as a yellow solid (92%). M.p. 242–245°; λ_{max} nm. 235. 281. 304. 313. 328. 422; λ_{min} nm. 255. 292. 309. 323. 372. This spectrum is identical to that described by Bradsher and Dutta.[14]

Reduction of the benzacridizinium salts (**6**) *with sodium borohydride* (±)-*norcoralydine*. A suspension of **6** (R = OMe). (0·25 g) in 2N HCl (120 ml) was neutralized with 0·880 ammonia soln. MeOH (50 ml) was added to the mixture and $NaBH_4$ (1·0 g) was added to the warm (50°) soln. The mixture was maintained at the same temp for $\frac{1}{2}$ hr. after which time the MeOH was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2:ether (1:1). (4 × 25 ml). and the combined dried extracts evaporated to yield (±)-norcoralydine (0·18 g) m.p. 155–157° (EtOH). (Lit.[3] 157–158°). A mixed m.p. with authentic sample[15] was undepressed.

(±)-*Tetrahydro*-ψ-*berberine* was prepared from **6** (RR = CH_2O_2) by the above method and was obtained as a pale yellow solid (80%) m.p. 176–177° (EtOH). (Lit.[22] m.p. 177°); λ_{max} (ε) nm. 225 sh (6980). 289 (3200). ν_{max} cm^{-1}. 2780. 1610. *m/e* (Rel. Int.). 339 (20). 338 (6). 174 (9). 164 (100). 149 (11). 121 (14). (Found: C. 70·4; H. 6·4; N. 4·3. Calc. for $C_{20}H_{21}NO_4$: C. 70·8; H. 6·2; N. 4·2%).

Separation of the diastereomeric O-*acetates of* 2.3.10.11-*tetramethoxy*-5-*hydroxyberbine* (**4**. R_1 = OCH_3.

R_2 = OH). The crude base (0·3 g) m.p. 180–190° obtained by basification of an aqueous soln of its hydrochloride was dissolved in Ac_2O (3 ml) and stood for 24 hr at room temp. then at 0° for a further 24 hr. The mixture was diluted with water. and. on basification with 2N ammonia soln. a yellow solid (0·31 g) was deposited. The solid was dissolved in hot EtOH and on cooling O-*acetate A* (**8b**) separated as pale yellow needles (0·17 g). m.p. 188–189°: λ_{max} (ε) nm. 227 sh (20.650). 284 (6600); ν_{max} cm^{-1}. 1715 (C=O). 1605; NMR ($CDCl_3$); 2·1 (3H. s. CH_3CO); 2·7–4·1 (7H. m. aliphatic H's); 3·90 and 3·95 (each s. 6H. 2 × MeO); 5·95 (1H. t. J = 3·0 Hz. $CH_2\underline{CH}OAC$); 6·62. 6·72. 6·85. 6 95 (each 1H. s. aromatic H). *m/e* (Rel. Int.). 413 (7). 353 (18). 352 (10). 164 (100). 149 (7). 121 (8). (Found: C. 66·9; H. 6·8; N. 3·6. $C_{23}H_{27}NO_6$ requires: C. 66·8; H. 6·6; N. 3·4%). The mother liquors from which O-*acetate A* separated were concentrated and on cooling white needles (0·12 g). m.p. 162–163°. of O-*acetate B* were obtained; λ_{max} (ε) nm. 227 sh (21.000). 284 (6300). ν_{max} cm^{-1}. 1735 (C=O). 1610; NMR ($CDCl_3$); 2·16 (3H. s. CH_3CO); 2·5–4·0 (7H. m. aliphatic H's); 3·88 and 3·90 (each s. 6H. 2 × MeO); 6·1 (1H. m. $CH_2CH\underline{O}AC$); 6·60. 6·66. 6·75. 6·85 (each 1H. s. aromatic H). *m/e* (Rel. Int.). 413 (6). 353 (16). 352 (9). 164 (100). 149 (6). 121 (8). (Found: C. 66·8; H. 6·7. $C_{23}H_{27}NO_6$ requires: C. 66·8; H. 6·6%).

Reduction of the O-*acetates with lithium aluminium hydride.* A soln of O-*acetate A* (0·15 g) in THF:ether (1:1. 25 ml) was added to a stirred suspension of LAH (0·5 g) in ether (25 ml). The mixture was then stirred at room temp for 3 hr. heated for a further 1 hr and then cooled. The excess reagent was destroyed by the addition of 30% sodium potassium tartrate soln. the clear soln decanted. diluted with water (20 ml) and the organic solvents evaporated under reduced pressure. The residue was extracted with CH_2Cl_2:ether (1:1. 3 × 15 ml). the dried extracts combined dried and evaporated to yield 2.3.10.11-*tetramethoxy-5-hydroxyberbine A* (**8b**) (0·11 g). m.p. 194–195° (EtOH). The m.p. of a mixture of this compound and that obtained by repeated recrystallization of the mixture of enantiomers (**4**, R_1 = OMe, R_2 = OH) was undepressed; ν_{max} (10% soln in $CHCl_3$. 0·1 mm). 3580–3450. 2780. 1610 cm^{-1}.

2.3.10.11-*Tetramethoxy-5-hydroxyberbine B* (**9b**) was prepared from O-*acetate B* by the above method as colourless prisms (77%) m.p. 175–177° (MeOH). ν_{max} cm^{-1} (10% soln in $CHCl_3$. 0·1 mm). 3540. 2780. 1610 cm^{-1}. λ_{max} (ε) nm. 227 sh (22.300). 284 (7800). (Found: C. 67·8; H. 6·8. $C_{21}H_{25}NO_5$ requires: C. 67·9; H. 6·8%).

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FRIEDELIN AND EPIFRIEDELINOL

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FRIEDELIN AND EPIFRIEDELINOL FROM THE BARK OF *PRUNUS TURFOSA* AND A REVIEW OF THEIR NATURAL DISTRIBUTION

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Plant. Prunus turfosa Kalkman—Rosaceae.

Isolation of triterpenoids from bark. Extracted with light petroleum. Extract contains two compounds (TLC, Al_2O_3, 5% HOAc in C_6H_6, R_f 0·35 and 0·46). Separated by chromatography on Al_2O_3: Fraction A, C_6H_6. Fraction B, 5% C_6H_6 in $ChCl_3$.

Fraction A, *friedelin* (0·09%), m.p. 261–262° (lit.,[1] 261–264°), $[\alpha]_D^{21°} = -19°$ (benzene); identical with authentic sample. (Found: C, 84·4; H, 11·8. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%.)

Fraction B, *epifriedelinol* (0·05%), m.p. 280–282° (lit.,[1] 280–282°), $[\alpha]_D^{21°} = +21°$ (benzene); identical with authentic sample. (Found: C, 84·0; H, 12·3. Calc. for $C_{30}H_{52}O$: C, 84·0; H, 12·2%.)

Friedelin and epifriedelinol are very abundant in Nature and frequently occur together; thus, for example, these two triterpenoids have been shown to be present in species of lichens,[2] in some oceanic green algae[3] and in certain types of peat[4] and brown coal.[5]

In plants, friedelin and epifriedelinol are often accompanied by friedelinol and by β-sitosterol, as well as by other triterpenoids such as β-amyrin. Table 1 surveys the plants which have been examined and shown to contain friedelin, the part of the plant studied is indicated and the table also lists the more important co-occurring triterpenoids. The results of this survey show that friedelin is not restricted to any particular plant family and thus any taxonomic conclusions are precluded. In addition to the plants listed in the table, nineteen species of the Gramineae family have recently been examined;[6] these also contain friedelin and related triterpenoids.

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TABLE 1

Plant family	Genus and species*	Source	Epifriedelinol	Friedelinol	β-Sitosterol	Related compounds	Reference
FAGACEAE	*Quercus robur* L.	Bark	—	+	+	Alnusenone, alnusenol, 20-hydroxydammar-24-en-3-one	7
	Quercus incana Roxb.	Bark	—	—	+	—	8
	Quercus suber L.	Bark	—	+	—	Cerin	9
	Quercus petrarea (Mattusehka) Liebl.	Bark	+	+	—	—	10
	Quercus championae Hook.	Leaves	+	+	+	β-Amyrenyl acetate, hop-17(21)-en-3β-yl acetate, hop-17(21)-en-3β-ol	11
	Quercus bambusaefolia	Leaves	+	+	+	—	12
	Quercus myrsinae	Leaves	+	—	—	—	12
	Quercus glauca	Leaves	+	—	+	—	13
	Castanopsis cuspidata (Thunb.) var. *sieboldii* (Makino) Nakai.	Bark	+	—	—	—	14
	Castanopsis eyrei Tuch.	Leaves	+	—	+	22-Hydroxyhopan-3-one	15
ROSACEAE	*Prunus nepalensis* Hort. ex C. Koch.	Bark	+	—	—	—	16
	Prunus turfosa Kalkman.	Bark	+	—	—	—	
	Pyrus communis L.	Bark	+	—	+	—	17
	Pyrus malus L.	Bark	+	—	+	—	18
	Pyrus pashia Buch.	Bark and leaves	—	—	+	—	19
	Photina glabra Dcne.	Bark	+	—	—	—	20
ERICACEAE	*Rhododendron metternichii* Sieb & Zucc.	Leaves	+	—	—	β-Amyrin	21
	Rhododendron cinnamomeum Wall.	Leaves	+	—	—	3β-10β-Epoxy-D: B-friedo-oleanone	22
	Rhododendron decipiens Lacaita.	Leaves	—	—	—	—	23
	Rhododendron formosum Wall.	Leaves	—	—	+	Dihydrotaraxerone	24
	Rhododendron farrerae Tate & Suet.	Leaves	—	—	—	—	25
	Rhododendron campanulatum D. Don.	Leaves	+	—	—	3β-10β-Epoxy-D: B-friedo-oleanane	26
	Rhododendron westlandii Hempsl.	Leaves	+	—	—	Cerin, 3β-5β-epoxy-3β-alnusane lupeol, α-amyrin, β-amyrin	27

VACCINIACEAE	*Vaccinium bracteatum* Thunb.	Leaves	+	—	—	—	28
EUPHORBIACEAE	*Euphorbia antiquorum* Forsk.	Stem	+	—	—	Taraxerol, taraxerone, euphol	29
	Euphorbia hirta L.	Stem	—	—	—	β-Amyrin	22, 30
	Euphorbia neriifolia L.	Leaf and stem	+	+	—	β-Amyrin, taraxerol	31
	Baccaurea sapida Muell.	Bark	+	—	+	—	32
	Bridelia stipularis Blume.	Bark	—	—	+	—	33
	Bridelia micrantha Baill.	Bark	+	—	—	Taraxerone, taraxerol	34
	Putranjiva roxburghii	Whole plant	—	+	—	3α-Hydroxyfriedelan-7-one	35
	Bischofia trifoliata (Roxb.) Hk. f.	Leaves and stem	+	+	+	—	36
	Antidesma bunias Spreng.	Leaves and stem	+	—	+	Dammara-20,24-dien-3-β-ol	37
	Sapium discolor Muell.-Arg.	Leaves	+	—	—	—	37
	Pedilanthus calcaratus Schlecht.	Whole plant	—	—	—	—	38
	Pedlianthus tehuacamis TS Brandegee.	Whole plant	—	—	—	—	38
SALICACEAE	*Salix japonica* Thunb.	Bark	+	—	—	—	14
CELASTRACEAE	*Siphonodon australe* Benth.	Bark	—	—	—	Numerous friedelane derivatives	39
	Euonymus japonicus	Leaves	+	+	—	—	40
	Euonymus radicans	Leaves	—	+	—	—	41
	Euonymus alatus	Leaves	+	+	—	—	41
BALANOPHORACEAE	*Balanops australiona* F. Muell.	Bark	+	+	—	Cerin, betulinic acid	42
LEGUMINOSAE	*Dalbergia volubilis*	Wood	—	—	—	—	43
PINACEAE	*Pinus serotina* Hort.	Bark	+	—	—	—	44
COMPOSITAE	*Mikania cordata* (Burm. f) B. L. Robinson.	Root	+	—	—	—	45, 46
	Aster tataricus L.	Root	+	—	—	Shionone, shionol A	47
	Olearia paniculata	Bark	+	—	—	Ursolic acid, dammaradienyl acetate, oleanolic acid	48
	Inula helenium L.	Root	—	—	—	Dammaradienol, stigmasterol	49

TABLE 1.—*Cont.*

Plant family	Genus and species*	Source	Epifriedelinol	Friedelinol	β-Sitosterol	Related compounds	Reference
APOCYANACEAE	*Acokanthera spectabilis* (Sond.) Hook.	Leaves	—	—	—	—	50
MYRTACEAE	*Eugenia jambolana* L.	Bark	+	—	+	—	37
	Syzygium cordatum Hochst.	Wood and bark	+	—	+	—	51
ASCLEPIADACEAE	*Sarcostemma viminale* R. Br.	Whole plant	—	—	—	β-Amyrin	52
SAPINDACEAE	*Alectryon excelsum*	Bark	+	—	+	—	53
LILIACEAE	*Hemerocallis longituba* Miq.	Roots	—	—	+	—	54
LABIATAE	*Salvia glutinosa*	Gum exudate	—	—	—	11-α-Hydroxy-β-amyrin, β-amyrin, epialnusenol	55
RUBIACEAE	*Ophiorrhiza japonica*	Whole plant	—	—	+	—	56
	Antirrhoea chinensis (Champ.) Benth. & Hook.	Leaves	+	—	+	Ursolic acid, quinovic acid cincholic acid	57
MENISPERMACEAE	*Hypserpa nitida*	Leaves	—	—	—	—	58
STERCULIACEAE	*Abroma augustum* L.	Roots	—	—	—	—	59
AMARANTHACEAE	*Iresine pringlei* S. Watts.	Stems	—	—	—	Ceryl alcohol	60
MORACEAE	*Takini brosium*†	Bark	—	—	+	—	61
	Fiscus benghalensis Banyan.	Leaf	+	—	+	—	62
CUNONIACEAE	*Ceratopetalum apetalum* D. Don.	Bark	+	+	—	—	63

GUTTIFERAE	*Calophyllum brazilense*	Wood	—	—	+	β-Amyrin, betulinic acid	64
	Calophyllum inophyllum L.	Leaves	—	—	—	β-Amyrin, α-amyrin	65
BUXACEAE	*Pachysandra terminalis* Sieb. & Zucc.	Whole plant	+	—	+	Stigmasterol, pachysandiol A, pachysandiol B	66
RUTACEAE	*Citrus paradisi* Macfayden.	Fruit	—	—	+	—	67
	Citrus aurantium var. *sinensis*	Fruit	—	—	+	Citrostadienol, ceryl alcohol	68
HIPPOCASTANACEAE	*Aesculus hippocastanum* L.	Seeds	—	—	—	Butyrospermol, taraxerol, 3β,-22β-24,28-tetrahydro-16α,-12α-epoxyolean-12-ene	69
BROMELIACEAE	*Tillandsia usneoides* L.	Whole plant	—	—	—	Artostenone, cycloartenol, 3-25-dihydroxy 9:19-cyclolanosta-23-ene	70
ARALIACEAE	*Dendropanax trifidus* (Thunb.) Makino.	Leaves	+	—	—	3β,5β-Epoxy-3β-alnusane	71
VERBENACEAE	*Clerodendrum trichotomum* Thunb.	Bark	+	—	—	—	14
URTICACEAE	*Zelkova serrata* Makino.	Bark	—	—	—	—	14
SAPOTACEAE	*Madhuca butyracea*	Bark	—	—	+	α-Amyrin, β-amyrin, α-spinasterol	72

This table covers the literature 1927–1968 (inclusive) and is based upon *Chem. Ab.*
* Where the authority is not stated the original reference should be consulted.
† The botanical classification of this plant is uncertain.

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ESSENTIAL OIL FROM THE LEAVES AND INFLORESCENCE OF *OCIMUM GRATISSIMUM*

(*Phytochemistry*, 1971, 10, 3309)

M.p., mixed m.p., IR, NMR. *Glycerides of fatty acids.* Acid part consists of C_{24}-C_{32} straight-chain saturated fatty acids. Identified by GLC of methyl esters. *Unidentified compound.* (*A*) $C_{30}H_{50}O$, m.p. ~ 50°, IR ν^{KBr} 3400, 1030, 812 cm^{-1}, NMR $\delta^{TMS}_{CDCl_3}$ 0·75 (3H,s), 0·81 (3H,s), 0·86 (3H,s), 0·88 (3H,d, $J = 6·3$), 0·97 (6H,s), 1·60 (3H,s), 1·68 (3H,s), 3·25 (2H,m), 5·09 (1H,m), 5·25 (1H,m), benzoate, m.p. 144–145°, IR.

Acknowledgements—Thanks are due to Professor Y. Kitahara, Tohoku University, for the sample of cycloartenol.

Phytochemistry, 1971, Vol. 10, pp. 3309 to 3310. Pergamon Press. Printed in England.

LABIATAE

ESSENTIAL OIL FROM THE LEAVES AND INFLORESCENCE OF *OCIMUM GRATISSIMUM*

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(*Received* 28 *May* 1971)

Plant. Ocimum gratissimum L. Indigenous to Nigeria.

Previous studies. Major component of oil from specimens collected in Taiwan has been shown[1] to be eugenol (62%). This compound is the major component of the oil obtained from the leaves of a hybrid between *O. gratissimum* and *O. menthaefolium.*[2] The Nigerian *O. gratissimum* was reported[3,4] to contain thymol, but no eugenol. The remaining components of the oil from the Nigerian plant are reported here.[5]

RESULTS

Composition of oil from leaves (%):—α-pinene (2·6), camphene (4·0), β-pinene (0·6), α-terpinene: Δ^3-carene (4·1), myrcene (1·4), 1,8-cineole (1·1), α-terpinene (6·2), *p*-cymene (16·2) limonene (1·8) camphor (0·6), linalool (0·2), α-terpineol (2·4), $C_{10}H_{22}O$ (2·3), thymol (47·6), methyleugenol (1·7), methylisoeugenol (trace), caryophyllene (2·1), humulene (0·5), β-selinene (1·6), longifoline (3·0), clovene (trace). Oil from the flowers has essentially the same composition except the proportion of camphene is reduced.

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EXPERIMENTAL

The oils were obtained by steam distillation of freshly gathered leaves and flowers collected at the onset of flowering. Analysis was by GLC and GLC–MS (Column conditions: 15% carbowax 20 M on chromosorb W, 15% *Apiezon* L. on Universal B and 5% SE 30 gum rubber on Universal B. *Instrumental.* Pye 104 gas chromatograph coupled to MS 12 Mass-spectrometer). Individual compounds were characterized by direct comparison with the retention indices and fragmentation patterns of authentic specimens.

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LAURACEAE

n-PARAFFINS FROM THE LEAVES OF THREE GENERA OF LAURACEAE

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(*Received* 17 *March* 1971)

Abstract—*n*-Paraffins ranging from C_{16} to C_{33} were detected by gas chromatography from the leaves of *Cinnamomum camphora* Sieb., *Lindera obtusiloba* Blume, *Litsea japonica* Juss.).

Plants. Cinnamomum camphora Sieb., *Lindera obtusiloba* Blume, *Litsea japonica* Juss.

Occurrence. Hiroshima Prefecture, Japan.

Previous work. No work (concerning paraffin constituents).

Date. Cinnamomum camphora Sieb. (January 1971), *Lindera obtusiloba* Blume and *Litsea japonica* Juss. (September 1970).

Leaves. Crushed to pieces and extracted with *n*-hexane. Purification (column chromatography and molecular sieve 5A treatment).[1] Identification (GLC using two columns, SE-30-5%, Apiezon grease L-5%, column temperature 150–300°). The odd paraffins are in large amount (*Cinnamomum*, *Lindera*, *Litsea* are 84·2, 88·6, 57·9%, even ones are 13·8, 11·4, 42·1% respectively).

n-*Paraffins. Cinnamomum camphora* Sieb.: C_{16-19} (trace), C_{20}(0·2%), C_{21}(0·5), C_{22}(0·8), C_{23}(2·6), C_{24}(2·4), C_{25}(7·1), C_{27}(23·9), C_{28}(4·3), C_{29}(43·3), C_{30}(1·2), C_{31}(8·8), C_{32-33}(trace), *Lindera obtusiloba* Blume: C_{16}(1·1), C_{17}(0·3), C_{18}(1·3), C_{19}(0·4), C_{20}(1·3), C_{21}(0·4), C_{22}(1·3). C_{23}(1·4), C_{24}(1·3), C_{25}(3·9), C_{26}(1·9), C_{27}(25·6), C_{28}(1·6), C_{29}(45·1), C_{30}(1·6), C_{31}(11·5), C_{32-33}(trace). *Litsea japonica* Juss.: C_{19-22}(trace). C_{23}(0·6), C_{24}(2·1), C_{25}(3·4), C_{26}(7·0), C_{27}(14·4), C_{28}(18·8), C_{29}(23·8), C_{30}(14·2), C_{31}(14·8), C_{32}(trace), C_{33}(0·9).

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ISOLATION OF FRIEDELIN FROM *SECAMONE AFZELII*

(*Phytochemistry*, 1971, *10*, 1940)

Heartwood. An unidentified sterol, m.p. 73–74° and β-sitosterol (ether extract-chromatography on Al_2O_3). Leucocyanidin (acetone extract), microcrystalline powder (EtOAc–petrol), m.p. > 330° (darkens at 190°), $[\alpha]_D^{30}$ −8·6, λ_{max} 280 nm, colour reactions, preparation of enol acetate (Ac_2O + Py), m.p. 200°, $[\alpha]_D^{30}$ −14° and methyl ether ($Me_2SO_4 + K_2CO_3$, 36 hr), m.p. 260–263° and acid conversion to cyanidin chloride.

Acknowledgements—We are grateful to Prof. Dr. L. Hörhammer, Munich for the spectral data and direct comparison of our quercetin-3-arabinoside with authentic avicularin, and the Principal, J.I.P.M.E.R. for encouragement.

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ASCLEPIADACEAE

ISOLATION OF FRIEDELIN FROM *SECAMONE AFZELII*

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(*Received* 22 *December* 1970)

FOLLOWING a procedure which we normally use for the isolation of the alkaloidal fraction of plant organs, friedelin was obtained from the root of *Secamone afzelii* Schultes (= *S. myrtifolia* Benth.) This is the first mention of the occurrence of friedelin in *S. afzelii* although, in a recent review, Sainsbury[1] mentioned the fact that this compound and epifriedelinol frequently co-occur and are abundant in Nature. *Sarcostemma viminale* R.Br. is the only other member of the Asclepiadaceae reported to contain friedelin.

1 kg of the powered root was moistened with conc. ammonia solution and allowed to stand for 3 hr before it was exhausted with $CHCl_3$ in a soxhlet. The $CHCl_3$ extract was evaporated to dryness *in vacuo*, then the granular residue was triturated with warm N HCl (10 × 100 ml), and filtered before the acidic extract was shaken with $CHCl_3$ (5 × 100 ml). The $CHCl_3$ fraction was dried ($MgSO_4$) and evaporated to dryness to afford 760 mg of a brown residue (I). Preparative TLC of I (Silica gel; $CHCl_3$–alcohol (abs.)–acetone 90:5:5) gave, among others, a band (R_f 0·70) with bright blue fluorescence in UV and this was eluted with MeOH. Removal of the MeOH, *in vacuo*, gave a pale brownish residue 60 mg of which was taken up in benzene (20 ml), washed twice with dil. HCl (5 ml), dried ($MgSO_4$) and chromatographed on neutral grade Al_2O_3. The benzene fraction yielded friedelin (8 mg) which on TLC (Al_2O_3; 5% HOAc in C_6H_6) gave R_f 0·37 and red colour with 5% H_2SO_4 in EtOH after heating at 100° for 5 min. Recrystallization from benzene gave m.p. 261–262°; $[\alpha]_D^{21}$ − 20° (benzene); Mass M = 426·3869. $C_{30}H_{50}O$ requires M = 426·3861. IR(CCl_4) λ_{max} 1709 cm^{-1}. This material was identical in all respects to authentic friedelin.

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THE POTENTIAL CONTROLLED ANODIC OXIDATION OF 1,2-DIMETHOXY-4-PROP-1-ENYLBENZENE

(J.Chem.Soc.C., 1971, 2888)

The Potential-controlled Anodic Oxidation of 1,2-Dimethoxy-4-prop-1-enylbenzene

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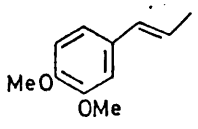
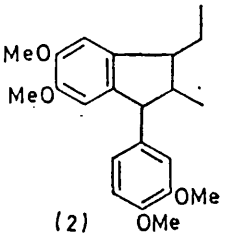
The anodic oxidation of 1,2-dimethoxy-4-prop-1-enylbenzene in acetonitrile solution, containing sodium perchlorate as supporting electrolyte, has been re-examined in order to investigate the reaction mechanism and to characterize the oxidation products.

In 1964 O'Connor and Pearl [1] described the controlled-potential oxidation of 1,2-dimethoxy-4-prop-1-enylbenzene (1) in acetonitrile solution, containing sodium perchlorate as supporting electrolyte. This work has often been cited subsequently as an example of the electrochemical oxidation of an aromatic olefin,[2] despite the fact that the products were only partially characterized.

This work has now been repeated on five occasions but none of the compounds previously described has been isolated, with the exception of the indane (2), formed by acid-catalysed dimerization. In our hands, the initial product of anodic oxidation (+1·0 V *vs.* S.C.E.) was a dark red perchlorate, which was stable in



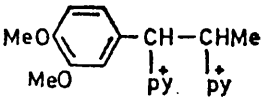
(1)



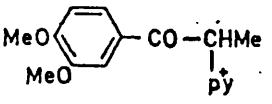
(2)

solution. An e.s.r. spectrum of this salt (in acetonitrile) exhibited a singlet peak at *g* 2·007, line-width 7 G. On basification the salt gives a complex polymeric mixture which could not be separated into individual components.

O'Connor and Pearl report that, in the presence of pyridine, the oxidation of (1) affords the salt (3), m.p. 110°. We confirm that this salt is formed, although our product had m.p. 205°, and was accompanied by smaller quantities of the perchlorate (4). This result indicates that at potential of +1·0 V (±0·1) both one- and two-electron oxidation processes occur simultaneously; the formation of compound (4) can be rationalized by assuming that the radical cation, initially formed by a one-electron oxidation of compound (1), undergoes attack by pyridine with concomitant aerial oxidation.

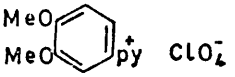


(3) 2 ClO_4^-



py = 1-pyridyl (4) ClO_4^-

Although styrene is not oxidized at anode potentials below +1·8 V (acetonitrile solution), veratrole exhibits an anodic wave of $E_{\frac{1}{2}}$ +1·3 V (one-electron transfer). The e.s.r. spectrum of the radical species so formed is very similar to that obtained from compound (1). In the presence of pyridine veratrole gives the salt (5) in high yield.



(5)

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% ethanol and i.r. spectra for Nujol mulls.

Oxidation of 1,2-*Dimethoxy*-4-*prop*-1-*enylbenzene* (1).—(a) *In the absence of pyridine.* The apparatus, conditions, and work-up procedure were as described by O'Connor and Pearl.[1]

(b) *In the presence of pyridine.* The reaction was carried out as described by O'Connor and Pearl.[1] After 16 h, the anolyte was evaporated to low bulk and poured on ice. The aqueous phase was decanted from an oily layer and the latter was then washed with ether. The residue was taken up in a small volume of 10% aqueous acetone; prisms of 1,2-*dimethoxy*-4-(1,2-*dipyridiniopropyl*)*benzene diperchlorate*

[1] J. J. O'Connor and I. A. Pearl, *J. Electrochem. Soc.*, 1964, **111**, 335.

[2] See for example, N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, 1968, **68**, 449.

(3) slowly separated. These were collected, washed with boiling acetone, and recrystallized from trifluoroacetic acid to give needles (20%), m.p. 205°, $\nu_{max.}$ 1638 ($C=\overset{+}{N}=$) and 1095 cm^{-1} (ClO_4^-), $\lambda_{max.}$ 245 nm (ε 2000), δ ($CF_3 \cdot CO_2H$) 9·2—8·9 (4H, m, 2- and 5-protons of pyridine rings), 8·8—7·8 (6H, m, remaining pyridine protons), 7·7—7·3 (3H, AMX system of dimethoxyphenyl group), 6·6 (1H, narrow d, *J* 12 Hz, ArC*H*py$^+$), 6·3 (1H, m, MeC*H*py$^+$), *ca.* 4·0 (6H, 2 × s, 2 × OMe), and 2·1 (3H, narrow d, *J* 6 Hz, Me) p.p.m. (Found: C, 47·2; H, 4·5; Cl, 13·1; N, 5·3. $C_{21}H_{24}N_2O_2,2ClO_4$ requires C, 47·2; H, 4·5; Cl, 13·2; N, 5·2%). Evaporation of the mother liquor from which compound (3) was obtained afforded *3′,4′-dimethoxy-2-pyridiniopropiophenone perchlorate* (4), which formed prisms (6%), m.p. 230° (from aqueous acetone), $\nu_{max.}$ 1680 (C=O), 1640 ($C=\overset{+}{N}=$), and 1090 (ClO_4^-) cm^{-1}, $\lambda_{max.}$ 225 (ε 10,000), 270sh (15,000), and 286 nm (16,500), δ ($CF_3 \cdot CO_2H$) 9·0 (2H, m, pyridine 2- and 5-protons), 8·8—8·0 (3H, m, remaining pyridine protons), 7·3—7·0 (3H, AMX system of 3,4-dimethoxyphenyl group), 6·85 (1H, d, *J* 7 Hz, MeC*H*py$^+$), *ca.* 4·0 (6H, 2 × s, 2 × OMe), and 2·15 (3H, d, *J* 7 Hz, Me) p.p.m. (Found: C, 51·6; H, 4·9; Cl, 9·3; N, 3·8. $C_{16}H_{18}NO_3,ClO_4$ requires C, 51·7; H, 4·9; Cl, 9·5; N, 3·8%).

Oxidation of Veratrole in the Presence of Pyridine.—A solution of veratrole (10 g) in acetonitrile (600 ml) containing sodium perchlorate (50 g) and pyridine (80 ml) was placed in the anode compartment * and electrolysed at an anode potential of $+1·5 \pm 0·2$ V. After 48 h the cell current had fallen almost to zero and the anolyte was separated and diluted with water (100 ml); the acetonitrile was evaporated. On cooling, needles of *3,4-dimethoxyphenylpyridinium perchlorate* (5) separated; recrystallisation from methanol gave prisms (11·8 g, 5·6%), m.p. 220°, δ ($CF_3 \cdot CO_2H$) 9·0 (2H, m, pyridine 2- and 5-protons), 7·3—7·1 (3H, m, phenyl protons) (in Me_2SO an AMX splitting pattern is revealed), 4·2 (6H, s, 2 × OMe), 8·8—8·0 (3H, m, remaining pyridine protons) (Found: C, 49·5; H, 4·5; N, 4·6. $C_{13}H_{14}NO_2,ClO_4$ requires C, 49·5; H, 4·45; N, 4·4%).

* The cathode solution had the same concentration except that no veratrole was added.

[1/529 *Received, April 14th,* 1971]

ALKALOIDS AND TERPENOIDS OF *BLEEKERIA VITIENSIS*

(*Phytochemistry*, 1972, *11*, 389)

Phytochemistry, 1972, Vol. 11, pp. 389 to 392. Pergamon Press. Printed in England.

SHORT COMMUNICATION

ALKALOIDS AND TERPENOIDS OF *BLEEKERIA VITIENSIS**

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(*Received* 6 *April* 1971)

Abstract—The alkaloidal components of the Ochrosiinae subtribe of the Rauvolfieae are reviewed and the phytochemical investigation of *Bleekeria vitiensis* has yielded ellipticine, 9-methoxyellipticine, isoreserpiline isoreserpiline-ψ-indoxyl and ursolic acid.

THE TAXONOMY of the thirty-six or so small trees of the Ochrosiinae (tribe Rauvolfieae, subfamily Plumerioideae of the Apocynaceae) is complex.[1] Individual species are often referred to the genera *Ochrosia*, *Excavatia*, *Bleekeria* or *Bleekaria* but there is a good deal of synonymy involved.

Table 1 lists the members of the Ochrosiinae which have been subjected to chemical scrutiny and shows the part of the plant examined, the alkaloids which have been characterized and the amount (where known) expressed as a percentage of the dry plant material. Unfortunately, only rarely have different parts of the same plant been studied and, in most cases, quantitative results have not been quoted. Nevertheless, all species contain indole alkaloids of which ellipticine, 9-methoxyellipticine, reserpine and isoreserpiline are the most important. Isoreserpiline occurs in eight of the ten species examined so far, 9-methoxyellipticine in six, ellipticine in five and reserpine in three.

Interest in the Ochrosiinae has been stimulated by the fact that ellipticine and 9-methoxyellipticine have wide spectrum antitumour activity, and it is the intention of the present study to evaluate the Ochrosiinae as a commercial source of these alkaloids. In this, the first of a series of papers, we report upon the extractives of *Bleekeria vitiensis* a small tree indigenous to the island of Fiji. In three separate experiments, the leaves and leaf stems, the bark and trunk wood and the roots and root bark have been studied; the results are included in Table 1.

Ellipticine is not present in the leafy material but occurs in the other organs of the plant whereas isoreserpiline is richest in the leaves but only present in trace amounts in the trunk and roots. 9-Methoxyellipticine is the major alkaloidal component and occurs in all parts of the plant examined. Moreover, the bark and wood of *Bleekeria vitiensis* would appear to represent the best natural source of this alkaloid yet discovered.

The only other alkaloid isolated from this plant is isoreserpiline-ψ-indoxyl, but whether this compound is a true natural product or merely an artefact of isoreserpiline is a matter

* Part I in a projected series "Extractives of the Ochrosiinae".

[1] G. H. SVOBODA, G. A. POORE and M. L. MONTFORT, *J. Pharm. Sci.* 1720 (1963).

TABLE 1

Plant and source	Part of plant	Ellipticine	9-Methoxy-ellipticine	Isoreser-piline	Other alkaloids	Ref.
Ochrosia elliptica Labill Florida, U.S.A.	Leaves and leaf stems	√(0·004%)	√(0·007%)	√(0·28%)	Elliptinine ($C_{20}H_{24}O_2N_2$)	4, 5
Ochrosia moorei F. Muel Australia (These are specimens of *O. elliptica* transplanted originally from Trinidad)		—	—	√	Elliptamine ($C_{24}H_{30}O_5N_2$)	6
Ochrosia coccinea (Tejsmann & Binnendijk) Kiq (syn. *Excavatia coccinea* (Tejsmann & Binnendijk) Mgf. New Guinea	Bark and leaves	—	√	—		5
		—	—	—	Reserpine	8
		—	—	√	Elliptamine	6
Ochrosia sandwicensis (ADC A Gray (syn. *Bleekaria calocarpa*) Hawaii	Leaves	√	√	—		4
	Trunk and root bark	√(0·04%)	√	—	10-Hunterburnine-α-methochloride (0·007%), 10-Hydroxydihydrocorynantheol methochloride	9
	Bark	—	—	—	N-(b)-Methylisoreserpilinium chloride	10
Ochrosia malculata Jacq. (syn. *Ochrosia borbonica* Gmel or *Cerbera undulata* Reunion Island	Bark	—	√(0·015%)	—	Reserpine	1, 2, 3
Ochrosia poweri Bailey Queensland, Australia	Leaves and twigs	—	—	√	Reserpine, powerine ($C_{21}H_{26}O_4N_2$), poweridine ($C_{24}H_{30}O_5N_2$), poweramine ($C_{23}H_{30}O_4N_2$), elliptamine	6
	Stem	—	—	√(0·3%)	Elliptamine, ochropamine ($C_{22}H_{26}O_3N_2$), ochropine ($C_{23}H_{25}O_4N_2$), powerchrine ($C_{22}H_{26}O_3N_2$)	12
Ochrosia oppositifolia (Lamk) K. Schum Mascarene and Seychelle Islands	Bark	—	√	—		7
Ochrosia Vieillardii Guil New Caledonia	Leaves	√(0·0079%)	—	√(0·085%)	10-Methoxydihydrocorynantheol	11
Ochrosia glomerate Valeton New Guinea	—	—	—	√	Elliptamine	6
Ochrosia silvation Dan New Caledonia	Trunk bark	√(0·13%)	—	√(0·58%)	Apparicine (0·012%)	13
Bleekeria vitiensis (Markgraf) A. C. Smith syn. *Ochrosia vitiensis* or *Excavatia vitiensis* Fiji	Leaves and leaf stems	—	√(0·003%)	√(0·05%)	Isoreserpiline-ψ-indoxyl (0·001%)	
	Bark and wood	√(0·001%)	√(0·083%)	√(0·002%)	Isoreserpiline-ψ-indoxyl (trace)	
	Roots and root bark	√(0·005%)	√(0·024%)	√(trace)	Isoreserpiline-ψ-indoxyl (trace)	

[2] C. C. J. CULVENOR and J. W. LODER, *Abstracts 152nd Meeting of Amer. Chem. Soc.* p. 29. Med. Chem. Sect., New York (1966).
[3] J. POISSON and C. MIET, *Ann. Pharm. Franc.* **25**, 523 (1967).
[4] S. GOODWIN, A. F. SMITH and E. C. HORNING, *J. Am. Chem. Soc.* **81**, 1903 (1959).
[5] J. W. LODER, *Austral. J. Chem.* **19**, 1947 (1966).
[6] F. A. DOY and B. P. MOORE, *Austral. J. Chem.* **15**, 548 (1962).
[7] A. BUZAS, M. OSOWIECKI and O. SCHINDLER, *Compt. Rend.* **247**, 1390 (1958).
[8] E. MACKO and R. F. RAFFAUF, *J. Med. Pharm. Chem.* **2**, 585 (1960).
[9] W. JORDAN and P. J. SCHEUER, *Tetrahedron* **21**, 3731 (1965).
[10] P. J. SCHEUER and J. T. H. METZGER, *J. Org. Chem.* **26**, 3069 (1961).
[11] C. KAN FAN, B. C. DAS, P. POTIER and M. SCHMID, *Phytochem.* **9**, 1351 (1970).
[12] B. DOUGLAS, J. L. KIRKPATRICK, B. P. MOORE and J. A. WEISBACH, *Austral. J. Chem.* **17**, 248 (1964).
[13] J. P. COSSON and M. SCHMID, *Phytochem.* **6**, 1353 (1970).

for conjecture. Isoreserpiline-ψ-indoxyl has been reported to co-occur with isoreserpiline in *Aspidosperma discolor*[14] but the compound has not been isolated before from members of the Ochrosiinae.

Bleekeria vitiensis has also been examined for non-alkaloidal compounds; the leaves contain a large amount of waxes which form a complex mixture. GLC analysis shows at least twelve components. The bark and root bark also contain waxy materials although in much smaller quantities than the leaves. Phenolic derivatives were not found in amounts sufficient for characterization but the triterpenoid ursolic acid was isolated from the leaves in 0·34% yield.

EXPERIMENTAL

All m.ps are uncorrected. SiO_2 refers to MN silica gel and Al_2O_3 to Merck basic alumina grade 1.

Leaves and leaf stems. 3 kg extracted exhaustively first with petrol (60–80°) (A), then EtOAc (B) and finally with MeOH (C).

Extract A. Removal of the solvent gave dark green gum which was chromatographed on SiO_2 and eluted with petrol (60–80°) (1), 15% $CHCl_3$/petrol (2) and 20% $CHCl_3$/petrol (3).

(1) This afforded a gummy residue, GLC analysis of which showed at least 12 components. High vac. distillation afforded several fractions, one of which crystallized to give colourless solid, m.p. 53°. Precision mass measurement of this material indicated the molecular formula $C_{31}H_{64}$. Other fractions could not be purified but mass and IR spectroscopy showed the presence of hydrocarbon derivatives of high molecular weight. (2) Evaporation yielded a waxy solid which recrystallized from acetone as colourless prisms, m.p. 76°. (3) From this fraction a similar compound m.p. 70° (acetone) was obtained. Spectral analysis shows that both of these compounds are saturated aliphatic esters with molecular weights above 800.

Extract B. The solvent volume was reduced from 10 l. to approx. 2 l. and this was then re-extracted with 2 N HCl. Basification of the aqueous phase yielded 6 g of crude alkaloids. The residual EtOAc extract was evaporated almost to dryness and allowed to cool, whereupon a solid (11·3 g) separated. This was collected and purified by chromatography (SiO_2) and repeated recrystallization from EtOH affording, eventually, colourless needles of ursolic acid, m.p. 276–278°. Further purification by sublimation gave material m.p. 280–282° (lit.,[15] 280°) (Yield 10 g, 0·34%). R_f 0·4 SiO_2, 5% MeOH/$CHCl_3$ (red colour when developed with 50% H_2SO_4/EtOH followed by heating at 100°). (Found: C, 78·9; H, 10·4. Calc. for $C_{30}H_{48}O_3$: C, 78·95; H, 10·5%.)

The crude alkaloids were purified by chromatography on Al_2O_3 and individual compounds were characterized as follows:

Isoreserpiline (eluting solvent 50% $CHCl_3$/petrol) 1·5 g (0·05%) colourless needles from ether m.p. 210° (lit.,[11] 213°) R_f 0·85 Al_2O_3 (red fluorescence in UV) (Found: C, 66·75; H, 6·95; N, 6·8. Calc. for $C_{23}H_{28}N_2O_5$: C, 67·0; H, 6·8; N, 6·8%.)

Isoreserpiline-ψ-indoxyl (60% $CHCl_3$/petrol) 30 mg (0·001%), pale yellow needles from ether, m.p. 243–247°; sublimation raised m.p. 250–252° dec (lit.,[14] 250–253°). R_f 0·83 Al_2O_3, $CHCl_3$ (bright green fluorescence in UV) (Found: G, 64·8; H, 6·5; N, 6·6. Calc. for $C_{23}H_{28}N_2O_6$: C, 64·5; H, 6·6; N, 6·5%.) This material was identical (mixed m.p., IR, NMR, TLC) with an authentic specimen.

9-Methoxyellipticine (4·8% MeOH/$CHCl_3$) 30 mg yellow prisms from EtOAc, m.p. 273–276°; further purified by sublimation, m.p. 283–285° (lit.,[4] 280–285°). R_f 0·7 Al_2O_3, 6% MeOH/$CHCl_3$ (red fluorescence in UV, maroon colour in I_2 vap.) (Found: C, 78·1; H, 5·8; N, 10·4. Calc. for $C_{18}H_{16}N_2O$: C, 78·2; H, 5·8; N, 10·1%.) This material was identical (mixed m.p., IR, NMR, TLC) with natural 9-methoxyellipticine.

Extract C. The combined extracts were evaporated and the residue dissolved in $CHCl_3$ and re-extracted with 2 N HCl. Basification of the aqueous extracts followed by chromatographic purification yielded a further 60 mg of 9-methoxyellipticine (total 90 mg, 0·003%). Trace amounts of isoreserpiline and isoreserpiline-ψ-indoxyl were also detected. The base free extract was evaporated to give a small quantity of ursolic acid (10 mg). Further evaporation afforded intractible tars.

Bark and wood. 8 kg extracted first with petrol to remove waxes and then with MeOH. The work-up procedure of the methanol extract parallels that of *C* above and yielded isoreserpiline (160 mg, 0·002%) and a mixture of ellipticine and 9-methoxyellipticine together with trace amounts of isoreserpiline-ψ-indoxyl. The mixture of ellipticine and 9-methoxyellipticine was separated by chromatography on Al_2O_3 eluting with $CHCl_3$. First fractions contained ellipticine (80 mg, 0·001%); pale yellow prisms from benzene m.p. 310–312° (lit.,[4] 311–315°) R_f 0·6, Al_2O_3, $CHCl_3$ (blue–green fluorescence under UV). (Found: C, 82·5; H, 5·9; N, 11·3

[14] N. DASTOOR and H. SCHMID, *Experientia* **19**, 297 (1963).
[15] R. E. CORBETT, H. YOUNG and R. S. WILSON, *Austral. J. Chem.* **17**, 712 (1964).

calc. for $C_{17}H_{14}N_2$ C, 82·9; H, 5·7; N, 11·4%.) From the remaining fractions 9-methoxyellipticine (6·65 g, 0·083%) was isolated.

Roots and root bark. 2 kg. This material was treated in the same manner as the bark and wood. In this way ellipticine (100 mg, 0·005%) and 9-methoxyellipticine (480 mg, 0·024%) were isolated. Additionally trace amounts of isoreserpiline and isoreserpiline-ψ-indoxyl were detected.

Acknowledgements—We are indebted to Dr. K. Jewers of the Tropical Products Institute, London for the gift of the plant materials, and to Professor P. J. Scheuer for a sample of 9-methoxyellipticine. Professor H. Schmid generously provided a specimen of isoreserpiline-ψ-indoxyl and Dr. W. H. Hui a sample of ursolic acid.

Key Word Index—Bleekeria vitiensis; Apocynaceae; ellipticine; isoreserpiline; indole alkaloids.

POTENTIAL CONTROLLED ANODIC OXIDATION OF 4-(3,4-DIMETHOXYBENZYL)-6,7-DIMETHOXYISOCHROMAN-3-ONE

(J.Chem.Soc.Chem.Comm., 1972, 718)

Potential Controlled Anodic Oxidation of 4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one

By M. SAINSBURY* and R. F. SCHINAZI
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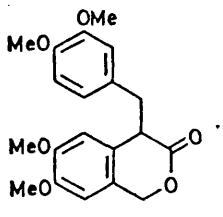
Summary Electrochemical oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one effects cyclization to a spiro-cyclohexadienone; evidence for the structure of the product is presented.

THERE is much interest in the mechanism and synthetic utility of the electro-oxidative cyclization of stilbene and dihydrostilbene derivatives[1] and the recent observation of the electrochemical cyclization of (±)-laudanosine[2] prompts us to report a similar ring-closure reaction of an isochroman-3-one derivative. As part of a study of the chemistry of this system, (1) was prepared and oxidized in acetonitrile solution containing sodium perchlorate and sodium carbonate at a platinum anode maintained at a potential of



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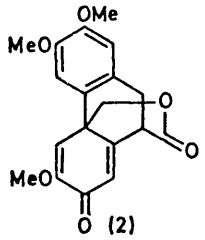

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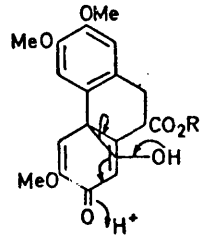

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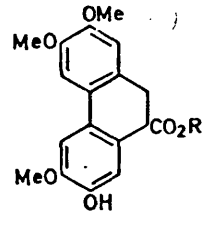

(4)

1·2 V (*vs.* Ag/AgCl as reference). The cyclized product (2) was quickly formed in 55% yield (2 g of starting material consumed in 2 h) *via* a two-electron oxidative reaction. The structure of the product, m.p. 256—257°, follows from analytical and spectroscopic data and the fact that on treatment with methanol and hydrochloric acid, under reflux, rearrangement to the methyl ester (4; R = Me), m.p. 170—171° occurs. When ethanol is used as the solvent, the ethyl ester (4; R = Et), m.p. 155—156°, is produced. The formation of the products (4; R = Me) and (4; R = Et) may be rationalized *via* the degradation of the intermediate alcohol (3; R = H or alkyl) as indicated.

(*Received, 17th April* 1972; *Com.* 636.)

[1] A. Ronlan and V. D. Parker, *Chem. Comm.*, 1970, 1567; see also A. Bewick and D. Pletcher, 'Organic Electrochemistry—Synthetic Aspects,' in 'Electrochemistry,' vol. 1, Specialist Periodical Reports, Chemical Society, London, 1970, ch. 4, p. 98 and references therein.

[2] L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, 1971, 93, 5941.

MINOR ALKALOIDS OF *BLEEKERIA VITIENSIS*

(*Phytochemistry*, 1972, *11*, 2337)

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SHORT COMMUNICATION

MINOR ALKALOIDS OF *BLEEKERIA VITIENSIS**

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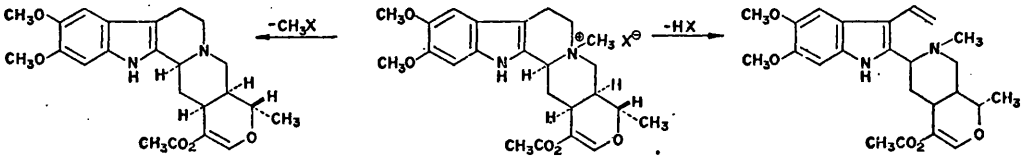
(*Received* 3 *February* 1972)

Key Word Index—*Bleekeria vitiensis*; Apocynaceae; indole alkaloids; 9-methoxyellipticine; holeinine; bleekerine; sterols.

Abstract—The chemical constituents of the stem-bark and wood of *Bleekeria vitiensis* are compared and the structure of a new alkaloid, bleekerine, is described.

IN A PREVIOUS paper[1] we showed that the combined stem-bark and wood of the Fijian plant *Bleekeria vitiensis* (Apocynaceae) A. C. Smith is the best natural source of the alkaloid 9-methoxyellipticine (0·083% based on dry plant material) yet reported. This compound has useful antitumour activity and, in order to confirm our results, we have examined a second specimen of the plant but this time the stem-bark and the wood were examined separately. The results are as follows: 9-methoxyellipticine is present in the bark and in the wood, although much more abundant in the former (0·165% vs. 0·006%). Ellipticine, isoreserpiline and isoreserpiline-ψ-indoxyl are also present in both parts of the plant and these alkaloids are accompanied by small amounts of sitosterol, stigmasterol and campesterol.

In addition, the bark yields the alkaloid holeinine (I), present as the mixed chloride–bromide. This alkaloid, previously isolated by Scheuer[2] from the related plant *Ochrosia sandwicensis*, was not detected in the first specimen of *Bleekeria vitiensis*.[1] On pyrolysis, holeinine forms isoreserpiline (II);[2] we have observed that this reaction is replicated in the mass spectrometer, giving rise to the spectra of isoreserpiline and the appropriate methyl halide. Moreover, a Hofmann-type elimination also occurs, affording the molecular species (III) or its equivalent, plus hydrogen chloride and hydrogen bromide. The presence of a molecular ion *m/e* 440·2310 ($C_{25}H_{32}N_2O_5$) is observed in the mass spectrum of holeinine and it is significant that the same ion is also present in the mass spectrum of a sample of



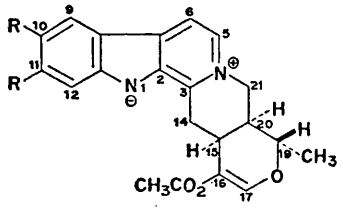
(II) (I) (III)

* Part II in the series "Extractives of the Ochrosiinae". For Part I see Ref. 1.

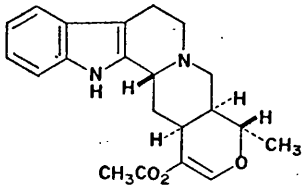
[1] K. N. KILMINSTER, M. SAINSBURY and B. WEBB, *Phytochem.* **11**, 389 (1972).
[2] P. J. SCHEUER and J. T. HAMAMOTO METZGER, *J. Org. Chem.* **26**, 3069 (1961).

holeinine obtained from *O. sandwicensis*. It is possible that the origin of this molecular ion is the, as yet unreported, alkaloid salt N(a)-methylholeinine, but because of the extremely low concentration in the plant it has not been possible to confirm this.

Another alkaloid, bleekerine $C_{23}H_{24}N_2O_5$ m.p. 276–277° (EtOH) $[\alpha]_{546nm}^{22.5}$ + 612 (MeOH), is found in the stem-bark of *Bleekeria vitiensis*; this molecule has not been described previously. The UV spectrum λ_{max}^{EtOH} (ϵ) 208 (14 000), 242 (14 900), 276 (9850), 336 (12 150), and 394 (5600) nm suggests a highly conjugated structure and bands at 1693, 1618, 1225, 1210 and 1185 cm^{-1} in the IR spectrum (KBr) demonstrate the presence of a β-alkoxyacrylic ester unit, similar to that of isoreserpiline.[3] Bleekerine does not contain a >NH function, although a band at 1630 cm^{-1} is indicative of a $>C=N^+=$ group. The molecular ion *m/e* 408 is the base peak of the mass spectrum which, apart from an $(M-15)^+$ ion (79·5%), shows little fragmentation and confirms the conjugated nature of the molecule. This mass spectrum is closely similar to that of alstonine (IV, R=H), *m/e* 348 (100%) (M^+), 333 (41·8%) $(M-15)^+$, and since on reduction, with $NaBH_4$ in methanol, bleekerine yields



(IV)



(V)

isoreserpiline, the structure of this new alkaloid must correspond to 10,11-dimethoxy-alstonine (IV, R=OCH_3). The NMR spectrum (CF_3CO_2H), which substantiates this structural allocation, is summarized in Table 1.

TABLE 1. SUMMARY OF THE NMR OF BLEEKERINE

δ	Multiplicity	No. of protons	Assignment
1·56	d (J = 6·0 Hz)	3	=CH–C$\underline{H}_3$
2·4–4·6	m	6	aliphatic protons
3·93	s	3	–$CO_2C\underline{H}_3$ and
4·12	s	6	2 x–$OC\underline{H}_3$
4·92	double d (J = 14·0, 7·3 Hz)	1	C_{21}–$\underline{H}$ (α)*
7·30	s	1	C–$\underline{H}_9$, C–$\underline{H}_{12}$,
7·70	s	1	C–$\underline{H}_{17}$
7·95	s	1	
8·20	s	2	$C_5\underline{H}$, C_6–$\underline{H}$

* The signal due to C_{21}–$\underline{H}$ (β) is superimposed upon that of C_{19}–$\underline{H}$ at $\delta \sim 4{\cdot}6$.

Oxidation of isoreserpiline with lead tetra-acetate, under similar conditions[4] to those whereby akuammigine (V) is converted into alstonine (IV, R = H), affords bleekerine in very low yield. Crude bleekerine contains traces of a further quaternary alkaloid salt which, in the mass spectrometer, gives rise to a molecular ion *m/e* 422·1842 ($C_{24}H_{26}N_2O_5$) together

[3] See for example B. GILBERT, *The Alkaloids* (edited by R.H.F. MANSKE), Vol. VIII, p. 335, Academic Press, New York (1965).

[4] E. WINTERFELDT, H. RADUNZ and T. KORTH, *Chem. Ber.* **101**, 318 (1968).

with ions due to methyl chloride and hydrogen chloride. Possibly this molecule is N(a)-methylbleekerine.

EXPERIMENTAL

M.p's are uncorrected. Al_2O_3 refers to Merck neutral grade 1 (column) or Merck GF_{254} Type E (TLC).

Wood. Pulverized dry wood (500 g) was extracted exhaustively with boiling EtOH (5 l.). Removal of the solvent gave a dark coloured residue (0·113 g). This material was chromatographed repeatedly on preparative Al_2O_3 TLC plates developing with 1% MeOH–$CHCl_3$. In this way 9-methoxyellipticine (30 mg, 0·006%), m.p. and m.m.p. 283–285° (lit.,[6] 280–285°) R_f 0·7 Al_2O_3, 6% MeOH–$CHCl_3$, was obtained. From the first TLC separation a band which ran with the solvent front was collected and eluted to give a crude mixture of sterols (5 mg). MS examination of this mixture revealed molecular ions at *m/e* 414·3844 ($C_{29}H_{50}O$) 412·3705 ($C_{29}H_{48}O$) and 400·3705 ($C_{28}H_{48}O$), which correspond to sitosterol, stigmasterol and campesterol respectively. GLC: 2·5% OV1 on chromasorb W, AW–DMCS 200°, R_ts (with respect to sitosterol) 1·0, 0·87, 0·74. These values are closely similar to those reported by Rowe[5] and the assignments are confirmed by reference to authentic samples. Trace amounts of ellipticine, isoreserpiline and isoreserpiline-ψ-indoxyl were also detected during the purification of 9-methoxyellipticine from the wood extract.

Bark. Finely divided dry stem-bark (500 g) was exhaustively extracted with ethanol (7 l.). After removal of the solvent, the residue (2·0 g) was chromatographed on Al_2O_3 eluting with petrol (60–80°)–$CHCl_3$ and $CHCl_3$–MeOH solvent systems. Three fractions *A*, *B* and *C* were collected: *A* 50% $CHCl_3$–petrol. The residue from this fraction was rechromatographed on Al_2O_3 to give, (i) a crude mixture of sterols (45 mg) in which stigmasterol, sitosterol and campesterol were shown to be present, and (ii) the alkaloid isoreserpiline contaminated with isoreserpiline-ψ-indoxyl. *B* 75–100% $CHCl_3$–petrol. On removal of the solvent, a brown semi-crystalline mass was obtained. This, when treated with MeOH, afforded pale yellow prisms (45·6 mg, 0·009%) of the alkaloid bleekerine m.p. 276–277° (EtOH), R_f Al_2O_3 (EtOH) 0·46 (bright blue fluorescence under UV), MS *m/e* 408·1690. $C_{23}H_{24}N_2O_5$ req. 408·1685 (Found: C, 67·8; H, 6·0; N, 7·1. $C_{23}H_{24}N_2O_5$ reqd. C, 67·6; H, 5·9; N, 6·9%). The MeOH mother-liquor was evaporated to yield a gum which crystallized when triturated with Et_2O, to give holeinine as the mixed chloride–bromide. This material was dissolved in water and treated with a few drops of $HClO_4$ affording holeinine perchlorate which was recrystallized from H_2O. Yield 82 mg (0·016%), m.p. 224–226° (lit.[2], 228–231°.) Comparison (IR and m.m.p.) with a sample prepared from an authentic sample of holeinine showed that the two specimens are identical. (Found C, 54·6; H, 6·0; N, 5·3. Calc. for $C_{24}H_{31}O_9N_2Cl$: C, 54·6; H, 6·0; N, 5·3%). The Et_2O layer, from which holeinine separated, was concentrated to yield isoreserpiline (25 mg) together with a further quantity of the sterol mixture (10 mg). *C* 5–100% MeOH/$CHCl_3$. Evaporation of this fraction gave a crystalline residue which recrystallized from EtOAc to give 9-methoxyellipticine (0·824 g, 0·165%) m.p. 280–282°. The mother-liquor on concentration and trituration with benzene yielded ellipticine (13 mg) contaminated with 9-methoxyellipticine. This mixture was separated and ellipticine characterized as previously described[1] (yield 9·5 mg, 0·002%). Total yield of isoreserpiline in bark 50 mg, 0·01%; total weight of mixed sterols 55 mg.

Reduction of bleekerine with $NaBH_4$. Bleekerine (10 mg) in MeOH was treated with $NaBH_4$ (20 mg) and the reaction mixture was heated under reflux until no further change was observed in the UV spectrum. Removal of the solvent gave a solid residue which was treated with H_2O (5 ml) and extracted with $CHCl_3$. Evaporation of the dry solvent phase yielded a gum which was purified by preparative TLC (Al_2O_3) eluting with 50% $CHCl_3$–petrol. Removal of a band R_f 0·6–0·8, followed by extraction with $CHCl_3$ and repeated chromatography afforded isoreserpiline (1·8 mg), identical with an authentic specimen (TLC, IR, MS).

Oxidation of isoreserpiline with lead tetra-acetate. A solution of isoreserpiline (20 mg) in HOAc (2 ml) maintained at 60° was treated dropwise with $Pb(OAc)_4$ (30 mg) in HOAc (10 ml). The addition was stopped when the UV spectrum of the product no longer showed the presence of the indole chromophore. Removal of HOAc under reduced pressure gave a dark red oil, this was dissolved in CH_2Cl_2 and shaken with 2 N Na_2CO_3 solution. The dried solvent layer was reduced in volume and applied to preparative TLC plates coated with Al_2O_3. The plates were developed with $CHCl_3$–MeOH (1:1) and viewed in UV light. A band R_f 0·6–0·85 was removed from the plates and worked up to yield a mixture of isoreserpiline and isoreserpiline-ψ-indoxyl, whereas a band at R_f 0·5–0·35 showing bright blue fluoresence was extracted to give a semi-solid product. This was rechromatographed, affording 0·8 mg of pure material identical (MS, GLC and m.m.p.) with bleekerine from *Bleekeria vitiensis*.

Acknowledgements—We are indebted to Dr. K. Jewers of the Tropical Products Institute, London for the gift of plant materials; to Professor P. J. Scheuer for a sample of holeinine and to Professor E. Wenkert for a specimen of alstonine. This work is sponsored by a grant from the Cancer Research Campaign.

[5] J. W. Rowe, *Phytochem.* **4**, 1 (1965).
[6] S. Goodwin, A. F. Smith and E. C. Horning, *J. Am. Chem. Soc.* **81**, 1903 (1959).

A NEW SYNTHESIS OF ELLIPTICINE

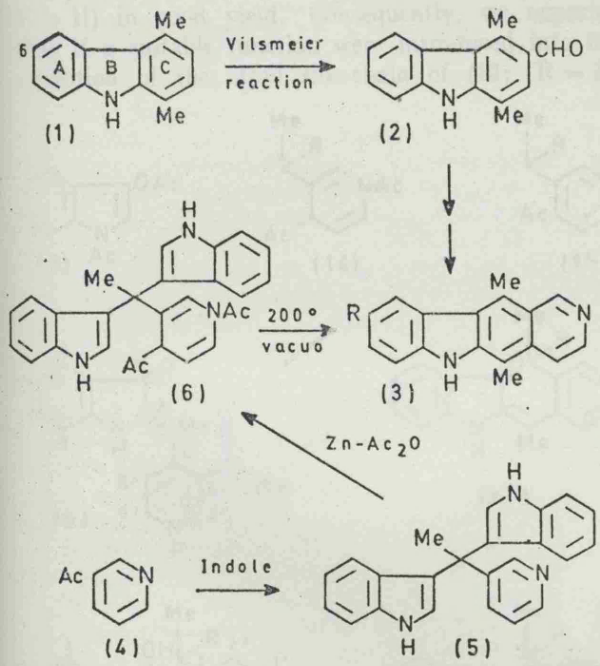
(J.Chem.Soc.Perkin 1, 1972, 2264)

A New Synthesis of Ellipticine

By K. N. Kilminster and M. Sainsbury,* School of Chemistry and Chemical Engineering, Bath University, Claverton Down, Bath, Somerset

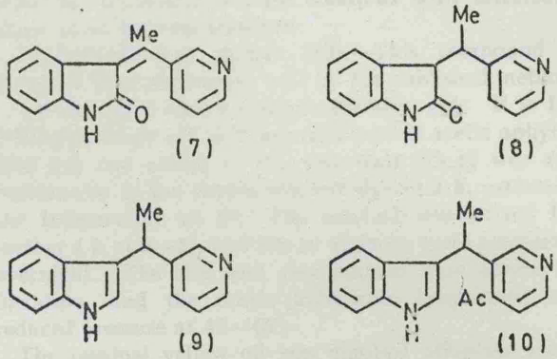
The tumour-inhibiting alkaloid ellipticine has been synthesized from indolin-3-one and 4-acetyl-3-(1-methoxyethyl)pyridine in 4 steps. This potentially versatile synthesis was accomplished in an overall yield of 31% (based on indolin-3-one).

THE alkaloids ellipticine (3; R = H) and 9-methoxyellipticine (3; R = OMe), which are commonly found in plants of the genera *Ochrosia*[1] or *Aspidosperma*[2] (Apocynaceae), have stimulated much interest because of their antitumour and antileukemic activity.[3] Although several syntheses of ellipticine have been described these are either very lengthy, or else the overall yield is poor. The hitherto most useful approach[4] suffers from the disadvantage that in the initial step it is necessary to convert 1,4-dimethylcarbazole (1) into the 3-formyl derivative (2). Since, however, the 6-position of the carbazole is also susceptible to electrophilic attack, problems due to isomers result. These difficulties are increased if electron-donating substituents are present in ring A other than at C-6. Woodward's synthesis[5]



of ellipticine from indole and 3-acetylpyridine (4) is extremely simple, but unfortunately the pyrolysis of (6) proceeds in only 2% yield. Nevertheless, the use of indoles or indole derivatives as starting materials is very attractive, since this would permit access to many ellipticine derivatives which are available only with difficulty by conventional methods, and initially we sought to adapt Woodward's scheme in the hope of increasing substantially the overall yield.

3-Acetylpyridine was reacted with indolin-2-one in the presence of pyrrolidine to yield the unsaturated amide (7), or its geometric isomer, and this was reduced with sodium borohydride in aqueous methanol to the dihydro-derivative (8). We expected that (8) could be



converted into the indole (9) and this in turn treated with zinc and acetic anhydride to give, after oxidation, the acetylpyridine (10). Cyclization of (10) to a dihydroellipticine should then be straightforward.

Confusion exists in the chemical literature concerning the action of lithium aluminium hydride upon indolin-2-one and its 3-alkyl derivatives; some authors claim[6] that reduction to the corresponding indoline may be achieved, whereas others[7] indicate that the reduction either does not proceed at all or else only with extreme difficulty. We support the latter point of view, since reaction of the indolinone (8) with lithium aluminium hydride under a variety of conditions did not lead to significant reduction. Julia and his co-workers[8] have shown that the indolinone (11) may be reduced with diborane to the indoline (12), but we were unable to achieve reduction of the indolinone (8) under the same conditions. The reason for our failure is not clear and although other reagents, *e.g.* phosphorus penta-

[1] K. N. Kilminster, M. Sainsbury, and B. Webb, *Phytochemistry*, 1972, **11**, 389, and references cited therein.

[2] G. Büchi, D. W. Mayo, and F. A. Hochstein, *Tetrahedron*, 1961, **15**, 167.

[3] G. H. Svoboda, G. A. Poore, and M. L. Montfort, *J. Pharm. Sci.*, 1968, **57**, 1720; J. Le Men, M. Hayat, G. Mathé, J. C. Guillon, E. Chenu, M. Humblot, and Y. Masson, *European Clinical and Biol. Research*, 1970, **15**, 534.

[4] P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3842; see also K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Austral. J. Chem.*, 1967, **20**, 2715.

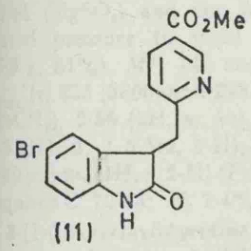
[5] R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Amer. Chem. Soc.*, 1959, **81**, 4434.

[6] P. A. S. Smith and T. Yu, *J. Amer. Chem. Soc.*, 1952, **74**, 1096.

[7] P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206; C. B. Hudson and A. V. Robertson, *Austral. J. Chem.*, 1967, **20**, 1699.

[8] M. Julia, F. Le Goffic, J. Igolen, and M. Baillarge, *Tetrahedron Letters*, 1969, 1569.

sulphide [9] and sodium in propanol,[10] have been used to reduce indolin-2-ones, we decided, after a brief study, to abandon this approach and to examine a route based upon indolin-3-one where problems due to the inertness of the carbonyl group are avoided.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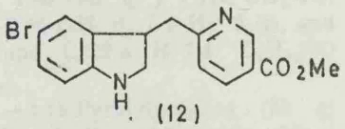
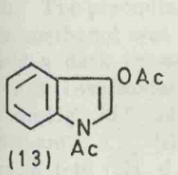

(12)

While indolin-3-one is very unstable in air, forming indigotin, the molecule may be handled conveniently as its 1,3-diacetyl derivative (13) and condensed with 4-acetyl-3-ethylpyridine (15; R = H) in the presence of aqueous alkali to give the unsaturated ketone (16; R = H). Attempts to cyclize this material to ellipticine failed, but we were able to show that reduction with sodium borohydride followed by acidification of the product (18; R = H) afforded the indole (19; R = H) in good yield. Consequently, we expected that if a suitable function were introduced into the α-position of the ethyl side-chain of (19; R = H)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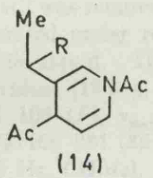
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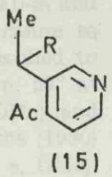
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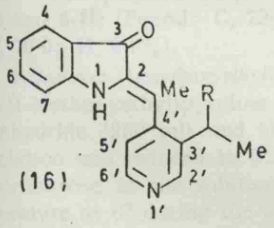
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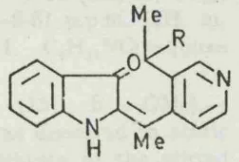
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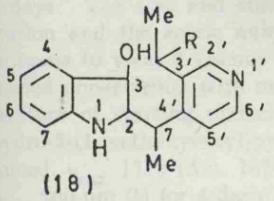
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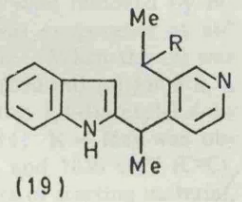
(19)

cyclization and oxidation to ellipticine would follow easily.[11]

Thus, the diacetyldihydropyridine (14; R = OMe) was prepared and oxidized to the acetylpyridine (15; R = OMe); * this material was condensed with 1-acetylindol-3-yl acetate (13) affording a mixture of two geometric isomers (16; R = OMe) and (17; R = OMe).† Reduction of either isomer with sodium borohydride, followed by acidification, gave the indole (19; R = OMe). This material was heated under reflux with aqueous hydrogen bromide, then neutralized, and the product absorbed onto silica gel. After standing for 6—7 h, the silica was removed and repeatedly extracted with chloroform to yield ellipticine 40%.

This new synthesis offers a rapid and efficient route to ellipticine and should provide access to a wide range of derivatives not available previously.

* 3-(1-Acetoxyethyl)pyridine was also prepared but it was not possible to convert this into the ester (15; R = OAc).

† A discussion of the stereochemical phenomena encountered in this work is given in ref. 12.

‡ 50% of starting material is recovered from this reaction which is considered to proceed by a disproportionation mechanism.[15]

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol, i.r. data refer to Nujol mulls unless otherwise stated: ^{1}H n.m.r. spectra were recorded either at 60 or 100 MHz for deuteriochloroform solutions with tetramethylsilane as an internal standard.

1-Acetylindol-3-yl Acetate (13).—This compound was prepared from anthranilic acid by the published method.[13]

1,4-Diacetyl-3-ethyl-1,4-dihydropyridine (14; R = H).—3-Ethylpyridine (23 g) [14] was dissolved in acetic anhydride (250 ml) and cooled to 0°; zinc dust (25 g) was added portionwise to the stirred solution during 3 h, maintaining the temperature at 0°. The mixture was stirred for a further 4 h at 0—5°, and left to warm to room temperature overnight. The zinc and zinc acetate were removed by filtration, and the acetic anhydride evaporated under reduced pressure at 40—45°.

The residual yellow oil was distilled affording starting material (10 g, b.p. 40° at 0·15 mmHg) and the dihydropyridine (14; R = H) (18 g), b.p. 126—128° at 0·1 mmHg (88%, based on 11·5 g of 3-ethylpyridine),‡ M^+, 193 (v weak), 149, and 136 (*P*), $\nu_{max.}$ 1708 (Ac), 1670 (NAc), and 1630 cm^{-1} (C=C), $\lambda_{max.}$ 260 nm, δ 1·05 (3H, t, *J* 6·5 Hz, CH_2*Me*), 2·0 (2H, q, *J* 6·5 Hz, *C*H_2Me), 2·15 (3H, s, Ac), 2·25 (3H, s, AcN), 3·75 (1H, d, *J* 5·0 Hz, 4-H), 5·0 (1H, m, 5-H), 6·70 (1H, m, 6-H), and 7·20 p.p.m. (1H, m, 1-H). This compound rapidly decomposed on standing and consequently satisfactory analytical figures were not obtained.

4-Acetyl-3-ethylpyridine (15; R = H).—The diacetyl compound (14; R = H) (10 g) in glacial acetic acid (100 ml) was treated dropwise with chromium trioxide (2 g) in water (20 ml) during 15 min. The mixture was stirred for 1 h at room temperature. Propan-2-ol (20 ml) was added and stirring continued for a further 15 min. The solvents were removed at 35° under reduced pressure, leaving

[9] H. Plieninger and G. Werst, *Angew. Chem.*, 1958, **70**, 272; S. Sugasawa, *J. Pharm. Soc.* (*Japan*), 1938, **58**, 139.

[10] G. Tacconi, S. Pietra, and M. Zaglio, *Farmaco* (*Pavia*) *Ed. Scientifica*, 1965, **20**, 470.

[11] See, for example, F. E. Ziegler, E. B. Spitzner, and C. K. Wilkins, *J. Org. Chem.*, 1971, **36**, 1759.

[12] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, in the press.

[13] D. Raileanu, O. Constantinescu-Simon, E. Mosanu, and C. Nenitzescu, *Rev. roumaine chim.*, 1967, **12**, 105.

[14] T. I. Fand and C. F. Lutomski, *J. Amer. Chem. Soc.*, 1949, **71**, 2931.

[15] J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, 1941, **60**, 119.

a dark green gum. This was extracted with saturated sodium hydrogen carbonate solution and ether. The ether extract was separated, washed with sodium hydrogen carbonate solution, and re-extracted with N-hydrochloric acid. The acid phase was washed with ether, made basic with solid sodium hydrogen carbonate, and the product was re-extracted into ether. The ethereal solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield *4-acetyl-3-ethylpyridine*, an oil (6·3 g, 81%), M^+, 149 and 134 (*P*), $\nu_{max.}$ 1690 (Ac) cm^{-1}, $\lambda_{max.}$ (ε) 225 (3800) and 278 (2100) nm, δ 1·20 (3H, t, *J* 7 Hz, *Me*CH_2), 2·58 (3H, s, Ac), 2·80 (2H, q, *J* 7 Hz, *CH_2*Me), 7·3 (1H, d, *J* 5 Hz, 5-H), 8·55 (1H, d, *J* 5 Hz, 6-*H*), and 8·60 p.p.m. (1H, s, 2-H) (Found: C, 72·5; H, 7·4. $C_9H_{11}NO$ requires C, 72·45; H, 7·4%).

3-(1-Chloroethyl)pyridine.—1-(3-Pyridyl)ethanol (20 g) (from a sodium borohydride reduction of 3-acetylpyridine) was dissolved in dry benzene (50 ml) and thionyl chloride (20 ml) was added dropwise, maintaining the temperature at 5—10°. The mixture was evaporated under reduced pressure to give a brown gum, which was taken up in cold water and washed with ether. The aqueous solution was made basic with solid sodium hydrogen carbonate and extracted with ether. The ethereal solution was washed, dried ($MgSO_4$), and evaporated under reduced pressure to yield the chlorinated compound as a mobile unstable brown liquid (22 g, 96%), $\nu_{max.}$ 650 cm^{-1}.

3-(1-Methoxyethyl)pyridine.— 3-(1-Chloroethyl)pyridine (22 g) was added to dry methanol (150 ml) containing sodium (5 g). The mixture was heated under reflux for 5 h. The precipitated NaCl was removed by filtration and the methanol was evaporated under reduced pressure to yield a dark brown mobile liquid. This was distilled to give *3-(1-methoxyethyl)pyridine* (16·5 g, 78%), b.p. 57° at 4 mmHg, M^+, 137 and 106 (*P*), $\nu_{max.}$ 1100 (OMe) and 2800 cm^{-1}, $\lambda_{max.}$ (ε) 255 (2110), 261 (2210), and 268 (1930) nm, δ 1·40 (3H, d, *J* 6·5 Hz, CH*Me*), 3·20 (3H, s, OMe), 4·33 (1H, q, *J* 6·5 Hz, *CH*Me), 7·15—7·40 (1H, m, 5-H), 7·55—7·80 (1H, m, 4-H), and 8·50—8·61 p.p.m. (2H, m, 2- and 6-H) (Found: C, 70·0; H, 8·1. $C_6H_{11}NO$ requires C, 70·0; H, 8·0%).

4-Acetyl-3-(1-methoxyethyl)pyridine (15; R = OMe).—3-(1-Methoxyethyl)pyridine (16 g) was dissolved in acetic anhydride (250 ml) and the temperature of the stirred solution was reduced to 0°. Zinc dust (19 g) was added portionwise to the solution (3 h), maintaining the temperature at 0° during the addition and then for a further 4 h. The mixture was stirred at room temperature for 2 days. The zinc and zinc acetate were removed by filtration and the acetic anhydride was evaporated at 40° *in vacuo* to yield a viscous orange oil. When the oil was heated under reflux with methanol (200 ml) (*a*) for 5 h, a mixture of starting material and the 1,4-diacetyl-1,4-dihydro-3-(1-methoxyethyl)pyridine (14; R = Me) was obtained, $\nu_{max.}$ 1710 (Ac), 1670 (AcN), and 1630 cm^{-1} (C=C), $\lambda_{max.}$ 260 nm (*b*) for 4 days, a mixture of starting material, a small amount of (14; R = OMe) and the required 4-acetyl-3-(1-methoxyethyl)pyridine (15; R = OMe) was obtained. From the latter reaction, the methanol was removed and the residue was dissolved in chloroform and extracted with 2N-HCl. The aqueous fractions were made basic with sodium hydrogen carbonate and re-extracted with chloroform. Evaporation of the dried extracts gave an oil which was distilled to yield starting material (7 g), b.p. 50° at 2 mmHg, and *product* (15; R = OMe) (6·5 g, 63%), b.p. 86—90° at 0·1 mmHg, $\nu_{max.}$ 1700 (Ac) cm^{-1}, δ 8·92 (1H, s, 2-H), 8·7 (1H, d, *J* 5 Hz, 6-H), 7·4 (1H, d, *J* 5 Hz, 5-H), 3·3 (3H, s, OMe), 2·6 (3H, s, Ac), 4·78 (1H, q, *J* 6 Hz, Me*CH*), and 1·5 p.p.m. (3H, d, *J* 6 Hz, *Me*CH) (Found: C, 67·1; H, 7·3; N, 7·8. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%).

(Z)-2-[1-(3-Ethyl-4-pyridyl)ethylidene]indolin-3-one (16; R = H).—4-Acetyl-3-ethylpyridine (3 g) in 50% aqueous methanol (50 ml) containing potassium hydroxide (10 g) was added to the acetate (13) (4·3 g) in a nitrogen-purged flask. The vessel was tightly stoppered and left for 3 days at room temperature. Filtration under nitrogen then afforded the *ketone* (16; R = H) (4·2 g, 80%), orange rods, m.p. 205—210° (decomp.), M^+, 264 and 235 (*P*), $\nu_{max.}$ 1680 (CO), 1630 (C=C), and 3100 cm^{-1} (NH), $\lambda_{max.}$ (ε) 239 (16,900), 263 (26,200), 297 (13,400), and 470 (7700) nm, δ 8·2 (1H, s, 2′-H), 8·2 (1H, d, *J* 6 Hz, 6′-H), 7·0 (1H, d, *J* 6 Hz, 5′-H), 7·84 (1H, bs, NH), 7·66 (1H, m, 4-H), 7·36 (1H, m, 7-H), 6·9—6·5 (2H, m, 5- and 6-H_2), 2·56 (3H, s, CMe), 2·52 (2H, q, *J* 7 Hz, *CH_2*Me), and 1·16 p.p.m. (3H, q, *J* 7 Hz, CH*Me*) (Found: C, 77·0; H, 6·1; N, 10·6. $C_{17}H_{16}N_2O$ requires: C, 77·3; H, 5·9; N, 10·4%).

2-{1-[3-(1-Methoxyethyl)-4-pyridyl]ethylidene}indolin-3-one (17; R = OMe).—This reaction was carried out as for the indolinone (16; R = H) and yielded a mixture of orange *rods* (16; R = OMe), m.p. 181—182°, and green *needles* (17; R = OMe), m.p. 180—181°. The total yield (2·3 g) was 80%, M^+, 294 and 235 (*P*), $\nu_{max.}$ (green needles) 1690 (CO), 1635 (C=C), and 3120 cm^{-1} (NH), $\nu_{max.}$ (orange rods) 1685 (CO), 1630 (C=C), and 3180 cm^{-1} (NH), $\lambda_{max.}$ (ε) 238 (17,000), 262 (24,200), 295 (11,250), and 470 (7800) nm. The n.m.r. spectra are interpreted in the following paper [12] [Found: C, 73·4; H, 6·1; N, 9·4 (orange); C, 73·4; H, 6·15; N, 9·45 (green). $C_{18}H_{18}N_2O_2$ requires C, 73·5; H, 6·2; N, 9·5%].

2-[1-(3-Ethyl-4-pyridyl)ethyl]indolin-3-ol (18; R = H).—The indolinone (16; R = H) (500 mg) in 70% aqueous ethanol (40 ml) was warmed to 70° and treated with sodium borohydride. After 0·5 h the solvent was evaporated and the residue was partitioned between chloroform and water. Removal of the chloroform gave a sticky solid (490 mg, 96%) which crystallized from methanol as *needles*, m.p. 185—186°, M^+, 268 and 135 (*P*), $\nu_{max.}$ 3285 (NH), 3110 (OH), and 1025 cm^{-1} (C–O–), $\lambda_{max.}$ (ε) 245 (7850) and 300 (1865) nm, δ (Me_2SO) 8·35 (1H, d, *J* 5 Hz, 6′-H), 8·30 (1H, s, 2′-H), 7·3 (1H, d, *J* 5 Hz, 5′-H), 7·2—6·35 (4H m, 4-, 5-, 6-, and 7-H_4), 5·45 (1H, d, *J* 6 Hz, OH), 5·25 (1H, d, *J* 4 Hz, NH), 4·85 (1H, t, *J* 6 Hz, C*H*·OH), 3·70 (1H, m, NH·C*H*), 3·25 (2H, q, *J* 7 Hz, MeC*H*), 2·65 [2H, q, finely coupled *J* 7 Hz (2 Hz), *CH_2*Me], 1·3 (3H, d, *J* 7 Hz, *Me*CH), and 1·10 p.p.m. (3H, t, *J* 7 Hz, *Me*CH_2) (Found: C, 75·9; H, 7·5; N, 10·6. $C_{17}H_{20}N_2O$ requires C, 76·1; H, 7·5; N, 10·4%).

2-{1-[3-(1-Methoxyethyl)-4-pyridyl]ethyl}indolin-3-ol (18; R = OMe).—Reduction of the enone (16; R = OMe) or (17; R = OMe) with sodium borohydride as described for the previous compound gave the title compound as an amorphous solid which was used directly.

2-[1-(3-Ethyl-4-pyridyl)ethyl]indole (19; R = H).—The alcohol (18; R = H) (100 mg) in dry methanol (50 ml) was saturated with hydrogen chloride. After 30 min, the solution was treated with an excess of potassium hydroxide pellets and the precipitated sodium chloride was removed by filtration. Evaporation gave a gum which was dissolved in chloroform and washed with brine to yield,

after removal of chloroform, a yellow oil. Continued extraction of the oil with hot light petroleum (b.p. 60—80°) followed by concentration of the extracts afforded cubes of the *indole* (19; R = H) (84%), m.p. 126—127° M^+, 250 and 235 (*P*), $\nu_{max.}$ 1620 (C=C), 1598, 3100, and 3040 cm^{-1} (NH), $\lambda_{max.}$ (ε) 270 (11,000), 283 (10,350), and 291 (9200) nm, δ 8·70 (1H, bs, NH), 8·26 (1H, s, 2′-H), 8·20 (1H, d, *J* 6 Hz, 6′-H), 6·96 (1H, d, *J* 6 Hz, 5′-H), 7·5—6·8 (4H, m, 4-, 5-, 6-, and 7-H_4), 6·4 (1H, bs, 3-H), 4·46 (1H, q, *J* 7 Hz, 7′-H), 2·70 (2H, q, *J* 7 Hz, CH_2Me), 1·66 (3H, d, *J* 7 Hz, CH*Me*), and 1·2 p.p.m. (3H, t, *J* 7 Hz, CH_2*Me*) (Found: C, 81·9; H, 7·1; N, 11·2. $C_{17}H_{18}N$ requires C, 81·6; H, 7·3; N, 11·2%).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (19; R = OMe).—The alcohol (18; R = OMe) was treated as in the previous experiment to yield the *methoxyindole* (19; R = OMe) (95%), plates, m.p. 165—166° (from aqueous ethanol), M^+, 280 and 233 (*P*), $\nu_{max.}$ 1620 (C=C), 1600, and 3140 cm^{-1} (NH), $\lambda_{max.}$ (ε) 269 (11,850), 283 (10,700), and 291 (9300) nm n.m.r.[12] (Found: C, 77·1; H, 7·3; N, 9·9. $C_{18}H_{20}N_2O$ requires C, 77·1; H, 7·2; N, 10·0%).

1-(3-*Pyridyl*)*ethyl Acetate*.—1-(3-Pyridyl)ethanol (50 g) in benzene (200 ml) was treated with acetyl chloride (50 ml) with vigorous stirring. After 30 min, the solvents were evaporated and the residue was dissolved in water and washed thoroughly with benzene. The aqueous phase was made basic with solid sodium hydrogen carbonate and extracted with ether. The combined ether extracts were washed with brine and then evaporated to give the crude *ester*, which was purified by distillation to yield an oil (57·5 g, 85%), b.p. 62° at 0·08 mmHg, $\nu_{max.}$ 1730 (OAc) and 1235 cm^{-1} (CO), $\lambda_{max.}$ (ε) 256, 262, and 270 nm, δ 8·7—8·5 (2H, m, 2- and 6-H_2), 7·8—7·55 (1H, m, 4-H), 7·35—7·10 (1H, m, 5-H), 5·90 (1H, q, *J* 6·5 Hz, C*H*Me), 2·05 (3H, s, OAc), and 1·55 p.p.m. (3H, d, *J* 6·5 Hz, CH*Me*) (Found: C, 65·35; H, 6·6. $C_9H_{11}NO_2$ requires C, 65·45; H, 6·7%).

Reaction of 1-(3-*Pyridyl*)*ethyl Acetate with Zinc Dust and Acetic Anhydride*.—1-(3-Pyridyl)ethanol (25 g) was treated with zinc dust and acetic anhydride as previously described. Removal of the acetic anhydride yielded a thick orange gum, the i.r. spectrum of which indicates that it is a dimeric structure.[15] Several attempts were made to carry out the disproportionation reaction but these failed.

Attempted Cyclizations on the Methoxy-indole (19; R = OMe).—The following reagents were tried: polyphosphoric acid, polyphosphoric ester, boron trifluoride–acetic anhydride,[16] sodium di-isopropylamide,[17] and sodium–potassium alloy.[18] All these attempts failed to yield ellipticine or its derivatives, giving only starting material or complex mixtures.

Ellipticine (3; R = H).—The indole (19; R = OMe) (400 mg) was dissolved in water containing hydrogen bromide 60% and heated under reflux until no further change was observed in the u.v. spectrum (4 h). The orange solution was made basic with ammonia and extracted with chloroform. The chloroform extracts were left over silica gel (10 g) for 6—7 h. The silica was then removed and repeatedly extracted with boiling chloroform. Evaporation gave a residue which crystallized when triturated with ether to yield pure ellipticine (140 mg, 40%), m.p. and mixed m.p. 309—312° (lit.,[4] 309—313°) (Found: C, 83·0; H, 5·6; N, 11·2. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%).

3-[1-(3-*Pyridyl*)*ethylidene*]*indolin-2-one* (7).—3-Acetylpyridine (12·1 g) and indolin-2-one (13·3 g) were heated under reflux in benzene (250 ml) and pyrrolidine (7·1 g) for 6 h in a flask equipped with a Dean–Stark trap. The dark red solution was evaporated to low bulk and left to cool, whereupon the *indolinone* (7) (19 g, 81%) crystallized and was collected as orange needles, m.p. 164—165°, M^+, 236 (*P*), $\nu_{max.}$ 1695 (CO·NH), 1630 (C=C), and 3200 cm^{-1} (NH), $\lambda_{max.}$ (ε) 220sh (10,400), 257 (12,800), and 305 (5300) nm, δ 2·8 (3H, s, MeC=C), 6·6—7·75 (6H, m), 8·55—8·75 (2H, m, 2′- and 6′-H_2), and 9·95 p.p.m. (1H, s, NH) (Found: C, 76·2; H, 5·2; N, 11·65. $C_{15}H_{15}N_2O$ requires C, 76·25; H, 5·1; N, 11·85%).

Reduction of the Indolinone (7) *with Sodium Borohydride*.—The foregoing unsaturated amide (2 g) in 50% aqueous ethanol (50 ml) was heated to reflux and treated with sodium borohydride (2 g). The pale yellow solution was evaporated to dryness, water was added, and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated to give a pale yellow gum (2 g). This could not be purified, although the physical characteristics are in accord with a mixture of diastereomers of the 3-[1-(3-pyridyl)ethyl]indolin-2-one (8), M^+, 238 (*P*), $\nu_{max.}$ 1715 (CO·NH) and 3160 cm^{-1} (NH), $\lambda_{max.}$ (ε) 255 (9500) and 261sh nm (8400), δ 1·3—1·35 (3H, 2 × d, *J* 7 Hz, *Me*CH), 3·0—3·3 (2H m, CO·C*H*·C*H*Me·), 6·7—7·5 (6H, m), 8·0—8·3 (2H, m, 2′- and 6′-H_2), and 9·50 p.p.m. (1H, s, NH). This material was then used directly.

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[2/1076 *Received*, 12*th May*, 1972]

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CONFIGURATIONAL AND CONFORMATIONAL ISOMERISM IN 2-γ-PICOLINYLIDENE INDOLIN-3(2H)-ONE DERIVATIVES

(J.Chem.Soc.Perkin 1, 1972, 2415)

Configurational and Conformational Isomerism in 2-γ-Picolinylidene-indolin-3(2*H*)-one Derivatives

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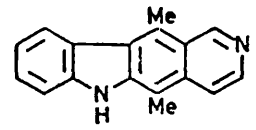
The reaction between indolin-3-one and 4-acetylpyridines gives rise to configurational and rotational isomers. Potential-energy barriers to rotation are calculated and the n.m.r. spectra of a number of derivatives are interpreted.

In the course of studies towards the synthesis of the alkaloid ellipticine (1),[1] 1-acetylindol-3-yl acetate was treated with the 4-acetylpyridine (2; R = OMe). Two products, green needles (m.p. 180—181°) and orange rods (m.p. 181—182°), were formed and separated by hand. Both products have the same electronic spectrum and mass spectrometry indicates them to be isomers of the molecular formula, $C_{18}H_{18}N_2O_2$. The orange substance is allocated structure (3; R = OMe), while the green isomer is represented as (4; R = OMe).

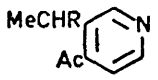
These assignments may be made with confidence, since in the former compound the methyl group joined to the double bond lies in the deshielding zone of the carbonyl function, and in the n.m.r. spectrum ($CDCl_3$) of the orange product the signal due to the olefinic methyl group is observed at lower chemical shift (δ 2·6 p.p.m.) than that of the corresponding resonance in the spectrum of the green material (δ 2·2 p.p.m.).

Figure 1A illustrates the n.m.r. spectrum of the green isomer (4; R = OMe) recorded at 36° and Figure 1B shows the high field portion of the spectrum of this compound measured at 87°. These results are rationalized as follows. Since the pyridine nucleus of the molecule (4; R = OMe) bears an asymmetric substituent,

[1] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.



(1)



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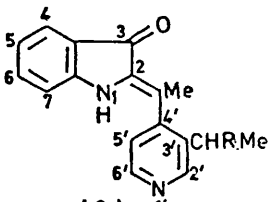

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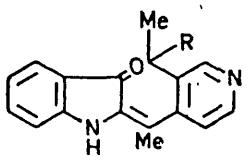


(4)

it is clear that restricted rotation about the single bond between the pyridyl group and the enone system allows diastereoisomerism at the lower temperature. As the temperature is increased this second chiral feature is gradually eliminated, until the observed spectrum becomes that of the racemate.

A similar phenomenon is observed in the case of the orange material (3; R = OMe) and, from the results of variable temperature experiments, it is possible to calculate the potential-energy barriers to rotation in both samples from the Arrhenius equation $k = k_0\exp(-E_a/RT)$, where the constants E_a (potential-energy barrier) and k_0 (frequency factor) can be deduced from the temperature-dependence of the n.m.r. spectra using the Gutowsky–Holm expression.[2] Thus for the (*Z*)-isomer (3; R = OMe) $E_a = 75{\cdot}4$ kJ mol^{-1} and for the (*E*)-isomer (4; R = OMe) $E_a = 77{\cdot}5$ kJ mol^{-1}.

In the reaction between 1-acetylindol-3-yl acetate and 4-acetyl-3-ethylpyridine (2; R = H), only one isomer (3; R = H) was isolated. Diastereoisomerism is not possible in this product and the interpretation of the observed n.m.r. spectrum is straightforward, in particular the olefinic methyl resonance appears as a 3-proton singlet (δ 2·56 p.p.m.).

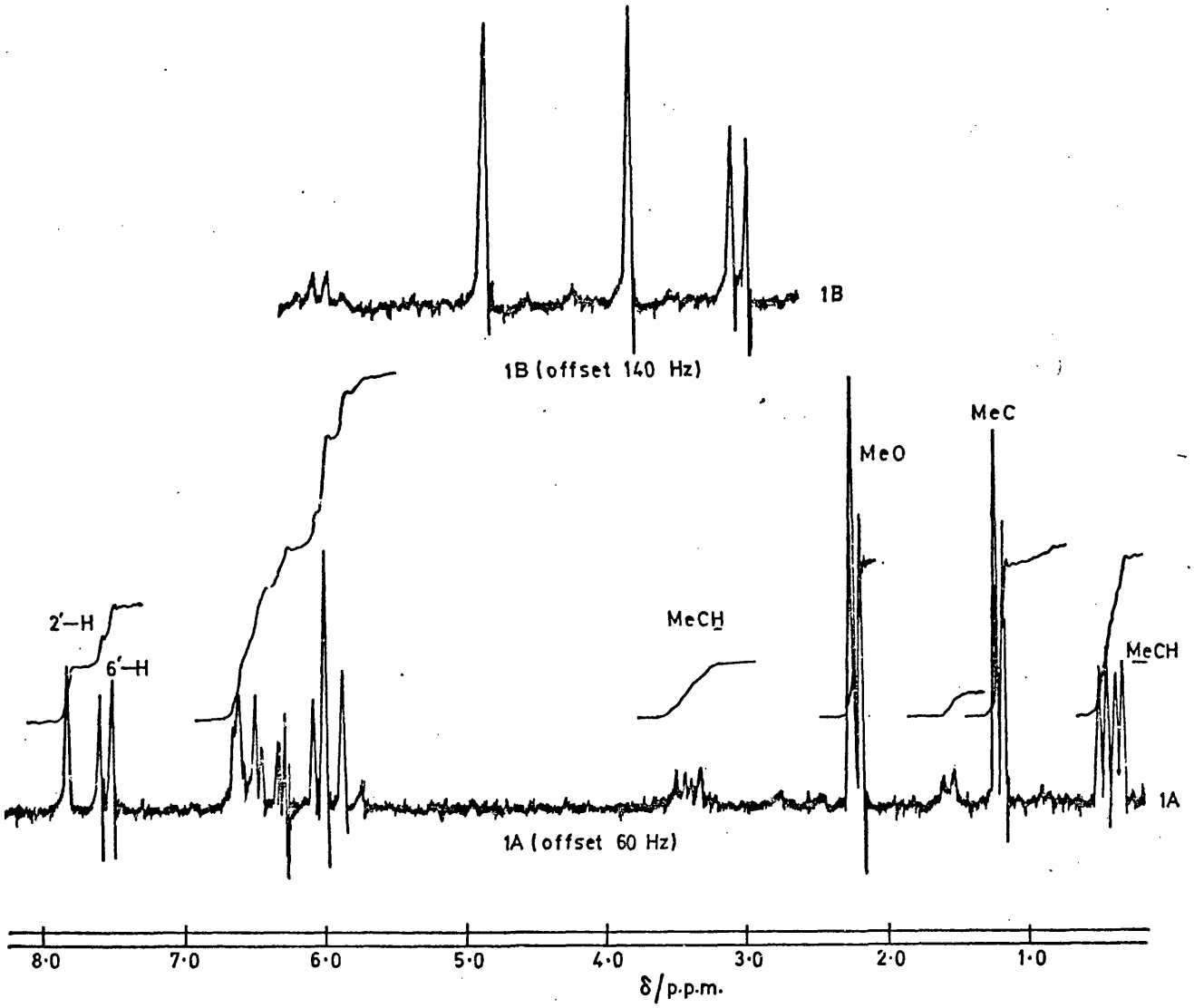


FIGURE 1

[2] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

When either isomer (3; R = OMe) or (4; R = OMe) is reduced with sodium borohydride in aqueous ethanol, the indole (5; R = OMe) is obtained. The n.m.r. spectrum of this substance shows that it is an equimolar mixture of two diastereomorphs, but this time the spectrum is unchanged by an increase * in temperature (see Figure 2).

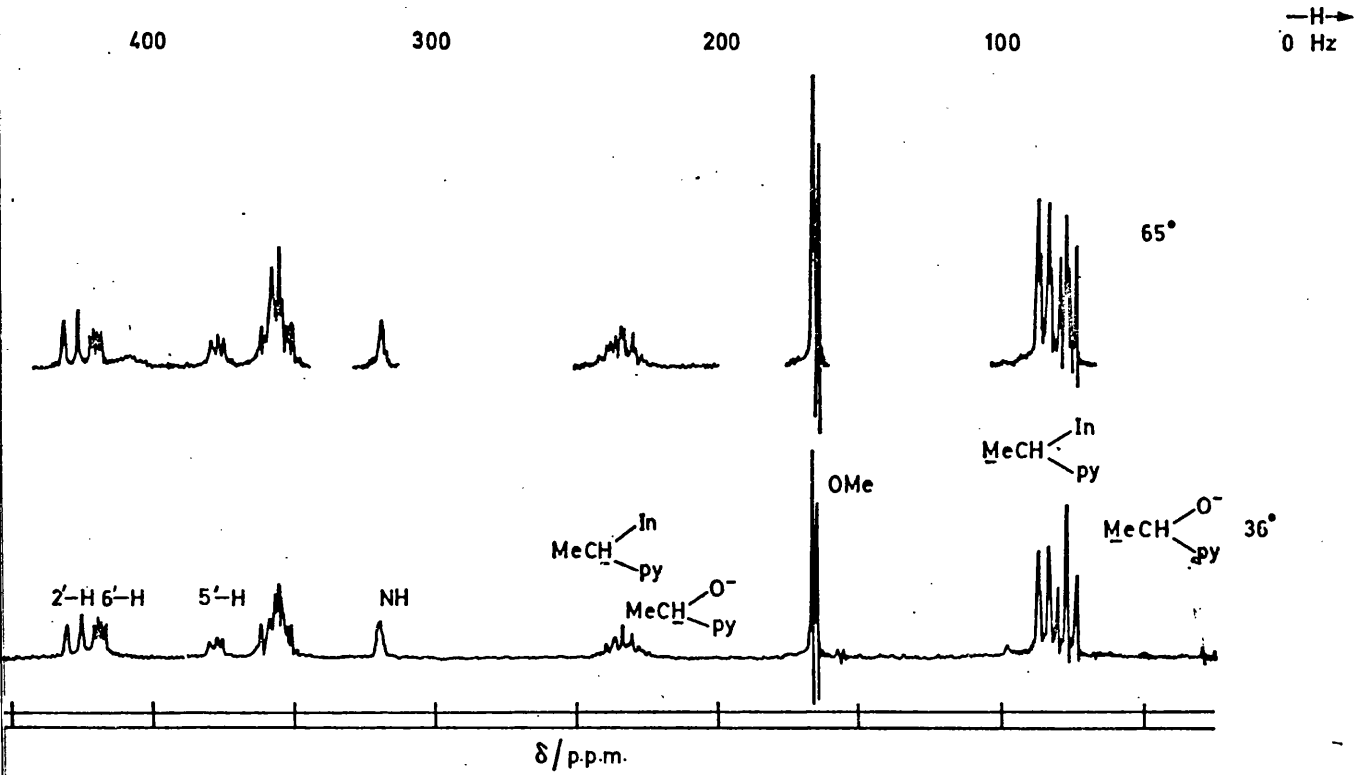
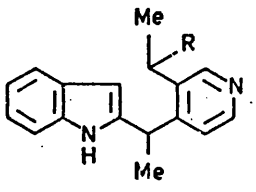
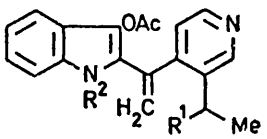


FIGURE 2

Since the proposed structure (5; R = OMe) for this indole contains two asymmetric carbon atoms the reason for the diastereoisomerism is obvious and, in



(5)



(6)

confirmation, it is significant that the n.m.r. spectrum of the indole (5; R = H) gives no evidence of isomers being present.

When either indolinone (3; R = OMe) or (4; R = OMe) is treated with acetic anhydride and triethylamine the rigid enone system is destroyed and a single product, the racemic *O*-acetate (6; R^1 = OMe, R^2 = H), is formed. The *NO*-diacetate (6; R^1 = OMe, R^2 = Ac) may also be isolated from these reactions and it is interesting that the signals due to the exocyclic methylene protons in the n.m.r. spectrum of this molecule appear as doublets at δ 5·66 and 5·75 p.p.m. (*J* 1·2 Hz), whereas the acetoxy methyl resonance is a singlet δ 2·27 p.p.m. [Corresponding signals in spectrum of the indole (6; R^1 = H, R^2 = Ac) are as follows: exocyclic methylene protons δ 5·70 and 5·76 (both d, *J* 1·1 Hz), acetoxymethyl 2·24 p.p.m.]. In the n.m.r. spectrum of the *O*-acetate (6; R^1 = OMe, R^2 = H) the exocyclic methylene protons resonate as singlets at δ 5·32 and 5·84 p.p.m., whereas the acetoxymethyl protons give rise to a singlet at δ 1·96 p.p.m. [In the n.m.r. spectrum of the indole (6; R^1 = R^2 = H), in dimethyl sulphoxide, the olefinic protons give rise to two singlets δ 5·26 and 6·0 p.p.m.; the hydrogen atoms of the acetoxy-group appear as a 3-proton singlet δ 1·6 p.p.m.]. The above spectra are not altered by change in recording temperature. It is probable that the deshielding influence of the carbonyl group of the *N*-acyl function is responsible for the chemical shift to lower field of one of the olefinic signals in going from the *O*- to the *NO*-diacetyl compounds, but the origin of the change in the line position of the acetoxy-signals is less easily quantified.

EXPERIMENTAL

N.m.r. spectra were recorded for $CDCl_3$ solutions unless stated otherwise. I.r. spectra were measured as Nujol mulls and u.v. data refer to solutions in 95% ethanol.

* Due to instrumental problems it was not possible to carry out variable temperature experiments below 10°.

N.m.r. Spectrum of 2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]-*ethylidene*}*indolin*-3-*one* (3; R = OMe) *at* 36°.—The spectrum showed signals at δ 8·68 (1H, s, 2′-H), 8·3 (1H, d, *J* 5 Hz, 6′-H), 7·75 (1H, bs, NH), 7·8—6·7 (5H, m, 5′-, 4-, 5-, 6-, and 7-H_5), *ca.* 4·4 (1H, 2 × interleaving q, C*H*Me), 3·30 and 3·24 (3H, 2 × s, OMe), 2·62 and 2·60 (3H, 2 × s, CMe), and 1·47 and 1·43 p.p.m. (3H, 2 × d, *J* 6 Hz). When the temperature is raised to 56° the appearance of the spectrum remains the same except the signals due to the MeO and CMe groups become singlets at δ 3·28 and 2·58 p.p.m., respectively, while the C*H*Me resonance becomes a quartet centred at δ 4·45 p.p.m. and the methyl reasonance a doublet at δ 1·44 p.p.m.

2-[1-(3-*Ethyl*-4-*pyridyl*)*vinyl*]*indol*-3-*yl Acetate* (6; R^1 = R^2 = H) *and* 1-*Acetyl*-2-[1-(3-*ethyl*-4-*pyridyl*)*vinyl*]*indol*-3-*yl Acetate* (6; R^1 = H, R^2 = Ac).—The indolin-3-one (3; R = H) (2·0 g) was heated under reflux with acetic anhydride (40 ml) and triethylamine (10 ml) for 1 h, during which time the colour of the solution changed from deep orange to pale yellow. Evaporation left a yellow gum, which when triturated with ether afforded needles of the *acetate* (6; R^1 = R^2 = H) (1·1 g, 48%), m.p. 194—195° (from benzene), M^+, 306 and 235 (*P*), $\nu_{max.}$ 1710 (OAc), 1620 (C=CH_2), 1210 (C–O), and 3100 cm^{-1} (NH), $\lambda_{max.}$ (ε) 235 (15,350), 306 (14,400), and 308 (1375) nm, δ(Me_2SO) 10·5 (1H, bs, NH), 8·52 (1H, s, 2′-H), 8·45 (1H, d, 5 Hz, 6′-H), 7·16 (1H, d, *J* 5 Hz, 5′-H), 7·4—7·0 (4H, m, 4-, 5-, 6-, and 7-H_4), 5·84 and 5·32 (2 × 1H, s, C:CH_2), 2·5 (2H, q, *J* 7·3 Hz, CH_2Me), 1·66 (3H, s, OAc), and 1·16 p.p.m. (3H, t, *J* 7·3 Hz, CH_2*Me*) (Found: C, 74·5; H, 6·0; N, 9·0. $C_{19}H_{18}N_2O_2$ requires C, 74·5; H, 5·9; N, 9·1%).

Evaporation of the ethereal mother liquor from which the acetate (6; R^1 = R^2 = H) was obtained gave a yellow gum, this was extracted successively with hot light petroleum (b.p. 60—80°) (total 50 ml) and the extracts were treated with charcoal and evaporated to yield the *acetyl-acetate* (6; R^1 = H, R^2 = Ac), rosettes (800 mg, 31%), m.p. 102—103°, M^+, 348 and 235 (*P*), $\nu_{max.}$ 1715 (OAc), 1745 (NAc), and 1620 cm^{-1} (C:CH_2), $\lambda_{max.}$ (ε) 234·5sh (13,750), 280 (10,325), and 303 (7600) nm, δ 8·5 (1H, s, 2′-H), 8·34 (1H, d, *J* 5 Hz, 6′-H), 7·0 (1H, d, *J* 5 Hz, 5′-H), 8·2 (1H, m, 7-H), 7·6—7·2 (3H, m, 4-, 5-, and 6-H_3), 5·76 and 5·70 (2 × 1H, d, *J* 1·2 Hz, C:CH_2) 2·27 (2H, q, 7 Hz, CH_2Me), 2·52 (3H, s, NAc), 2·24 (3H, s, OAc), and 1·2 p.p.m. (3H, t, *J* 7 Hz, CH_2*Me*) (Found: C, 72·3; H, 5·7; N, 8·0. $C_{21}H_{20}N_2O_3$ requires C, 72·4; H, 5·8; N, 8·0%).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*vinyl*}*indol*-3-*yl Acetate* (6; R^1 = OMe, R^2 = H) *and* 1-*Acetyl*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*vinyl*}*indol*-3-*yl Acetate* (6; R^1 = OMe, R^2 = Ac).—These acetates were obtained from either indolinone (3; R = OMe) or (4; R = OMe) as described in the previous experiment. The *acetate* (6; R^1 = OMe, R^2 = H), pale yellow needles, had m.p. 173° [from light petroleum (b.p. 80—100°)], M^+, 336 and 262 (*P*), $\nu_{max.}$ 1710 (OAc), 1620 (C:CH_2), 1205 (C–O), and 3140 cm^{-1} (NH), $\lambda_{max.}$ (ε) 232 (14,000) and 310 (13,700) nm, δ 8·78 (1H, s, 2′-H), 8·68 (1H, bs, NH), 8·5 (1H, d, *J* 5 Hz, 6′-H), 7·16 (1H, d, *J* 5 Hz, 5′-H), 7·4—7·0 (4H, m, 4-, 5-, 6-, and 7-H_4), 5·84 and 5·32 (2 × 1H, s, C:CH_2), 4·48 (1H, q, *J* 6 Hz, C*H*Me), 3·14 (3H, s, OMe), 1·96 (3H, s, OAc), and 1·36 p.p.m. (3H, d, *J* 6 Hz, CH*Me*) (Found: C, 71·4; H, 6·0; N, 8·2. $C_{20}H_{20}N_2O_3$ requires C, 71·4; H, 6·0; N, 8·3%). The *acetyl-acetate* (6; R^1 = OMe, R^2 = Ac), cubes, had m.p. 126° [from light petroleum (b.p. 40—60°)], (30 mg, 23%), M^+, 378 and 262 (*P*), $\nu_{max.}$ 1710 (OAc), 1765 (NAc), and 1620 cm^{-1} (C:CH_2), $\lambda_{max.}$ (ε) 235sh (14,300), 279 (10,900), and 302sh (7400) nm, δ 8·78 (1H, s, 2′-H), 8·44 (1H, d, *J* 5 Hz, 6′-H), 7·06 (1H, d, *J* 5 Hz, 5′-H), 7·9 (1H, m, 7-H), 7·6—7·2 (3H, m, 4-, 5-, and 6-H_3), 5·75 and 5·66 (2 × 1H, d, *J* 1·2 Hz, C:CH_2), 5·54 (1H, q, *J* 6 Hz, C*H*Me), 3·15 (3H, s, OMe), 2·49 (3H, s, NAc), 2·27 (3H, s, OAc), and 1·36 p.p.m. (3H, d, *J* 6 Hz, CH*Me*) (Found: C, 69·7; H, 5·9; N, 7·35. $C_{22}H_{22}N_2O_4$ requires C, 69·85; H, 5·85; N, 7·4%).

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LYCORINE: STUDIES IN SYNTHESIS

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LYCORINE: STUDIES IN SYNTHESIS

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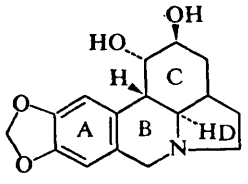
Abstract—Several unsuccessful attempts are described at the synthesis of the carbon-nitrogen skeleton of lycorine, utilising 1,2-dihydroisoquinoline intermediates.

All attempts that have been made so far to synthesise Amaryllidaceae alkaloids of the lycorine (1) type have failed, although compounds containing the pyrrolo[1,2,3-de]phenanthridine nucleus have been prepared. Compounds with ring C aromatic have usually been produced[1-4] by using the Pschorr ring-closure, whereas partially reduced derivatives, such as β-lycorane[5] (2) and (3),[6] have been obtained in sequences utilising a Diels-Alder reaction as the key step.



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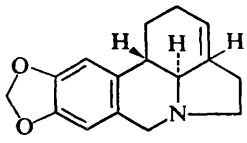

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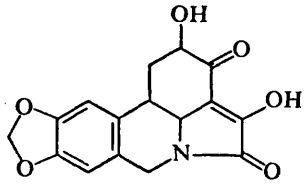

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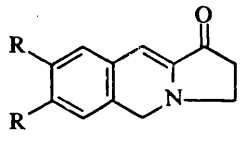
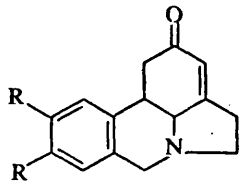
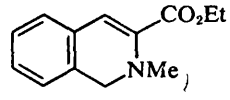


4a: R = H
4b: 2R = CH_2O_2

It has been established[7] that 1,2-dihydroisoquinolines may undergo electrophilic attack (e.g. by aldehydes) at C_4 and, in the derived imminium ion, nucleophilic attack at C_3. The approach to the synthesis of lycorine to be described here involved the preparation of the enamine (4b) followed by the introduction of a 3-carbon unit at C_4 capable of cyclisation with the CO function. It was envisaged that pyruvic aldehyde might provide such a fragment and that the tetracyclic compound (5b) may result. Since it is known[8] that ring C of lycorine is aromatised by light, oxygen or heat, a synthetic scheme that leaves the formation of ring C to a late stage seemed to possess considerable advantages. Since the completion of our work,[9] the enone (5b) has been prepared by an alternative method.[10]

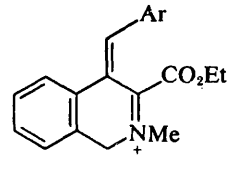


5a: R = H
5b: 2R = CH_2O_2

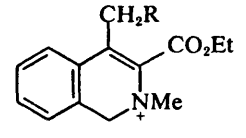


6

1,2-Dihydroisoquinolines that possess an electron-attracting group attached to the enamine system have not been investigated previously, so as a preliminary to our main aim, we studied some properties of the enamine (6). The methiodide of the readily available[11,12] methyl isoquinoline-3-carboxylate was reduced easily to 6 with sodium borohydride; even in aqueous ethanol solution, reduction did not proceed any further. The enamine (6) reacted normally with piperonal, veratraldehyde, glyoxylic acid and pyruvic aldehyde to give the 1,4-dihydro-4-benzylideneisoquinolines (7) or the aromatic quaternary salts (8). The 1,2-dihydroisoquinoline (6) failed, however, to react with the ethyl acetoacetate under the conditions of the Michael reaction.

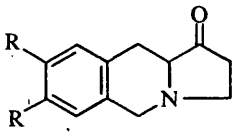


7a: Ar = 3,4-$CH_2O_2C_6H_3$
7b: Ar = 3,4-$(OMe)_2C_6H_3$

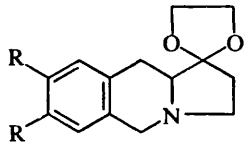


8a: R = 3,4-$CH_2O_2C_6H_3$
8b: R = 3,4-$(OMe)_2C_6H_3$
8c: R = CO_2H
8d: R = $COCH_3$

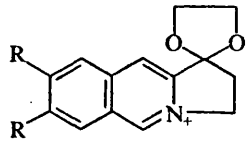
Encouraged by this result, attempts were made to prepare the model compound (4a). The known[13] amino ketone (9a) gave only black, polymeric material when attempts were made to dehydrogenate it with iodine, but the ethylene ketal (10a) when treated with iodine and sodium acetate gave a very small amount of a yellow solid, the spectral characteristics of which are in agreement with those expected for the required salt (11a). Insufficient material precluded any further investigation of 11, in particular its reduction with LAH.



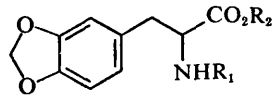
9a: R = H
9b: 2R = CH_2O_2



10a: R = H
10b: 2R = CH_2O_2



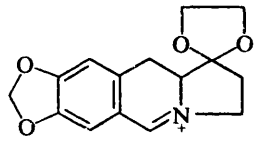
11a: R = H
11b: 2R = CH_2O_2



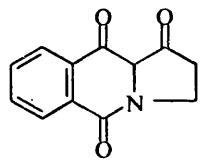
12a: $R_1 = R_2 = H$
12b: $R_1 = CH_2CH_2CN$; $R_2 = H$
12c: $R_1 = CH_2CH_2CO_2Et$; $R_2 = Et$

The tricyclic ketone (9b) was prepared in acceptable yield from 12a, the product obtained from the azlactone of piperonal. Alkylation with 3-bromopropiononitrile gave 12b, which with sulphuric acid and ethanol yielded the diester 12c. A Pictet-Spengler reaction on the latter, followed by a Dieckmann ring-closure of the resultant 1,2,3,4-tetrahydroisoquinoline-3-ester produced 9b, an unstable oil. Oxidation of the derived ketal (10b) with iodine as before gave a mixture of 13 and the required 11b. The former was converted into the latter by a more extended reaction time. Once again the overall yield of 11b was very small, so an alternative approach was investigated.

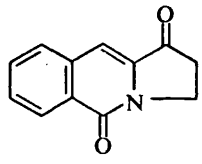
Whilst the above work was in progress, the preparations of 14 and 15 were reported[14] in a lengthy series of reactions. In repeating this work we have introduced some minor modifications (Experimental) involving glycine, rather than β-alanine, as starting material. Our spectral data for 14 indicated that the compound exists entirely in the enol form (16) and all efforts to ketalise, acetylate or benzoylate



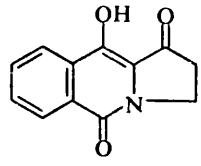
13



14



15

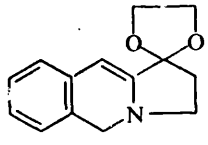


16

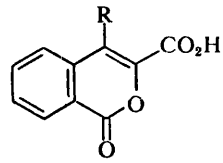
it, or to reduce it with LAH failed. However, ketalisation of 15 followed by reduction with LAH gave the required 1,2-dihydroisoquinoline (17). The yield was 2% in a thirteen stage sequence from glycine.

A shorter route has been developed from ethyl isocoumarin-3-carboxylic acid (18a),[15] which, with ethyl β-aminoproprionate afforded the isocarbostyril (19a). The derived ester (19b) was successfully cyclised to 15, and shown to be identical with the material obtained by Shamma and Novak.[14]

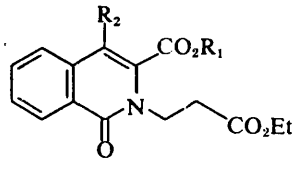
The reaction of the enamine 17 with pyruvic aldehyde was then subjected to an intensive study, but none of the hoped-for condensation product could be isolated from the complex reaction mixtures.



17

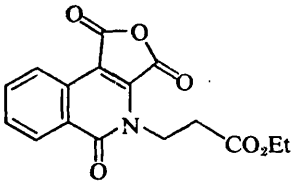


18a: R = H
18b: R = CO_2Et

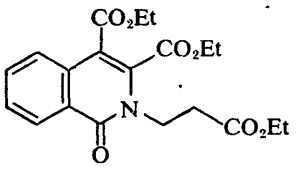


19a: $R_1 = R_2 = H$
19b: $R_1 = Et$, $R_2 = H$
19c: $R_1 = H$ $R_2 = CO_2Et$

In a final attempt to prepare the required C–N skeleton of lycorine, the acid-ester[15] (18b) was reacted with ethyl β-aminoproprionate, but the expected product (19c) was not obtained: the anhydride 20 was formed instead. Prolonged heating with ethanolic sulphuric acid yielded the tri

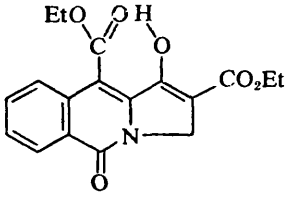


20



21

ester (21), which, with sodium ethoxide yielded a substance the spectral characteristics of which are in accord with the structure 22. However, in view of the many difficulties and poor yields of products, even in the model series, this type of approach to the synthesis of lycorine has been abandoned.



22

EXPERIMENTAL

All m.ps are uncorrected. UV spectra are reported for solns in EtOH (95%) and IR data refer to nujol mulls. NMR spectra were recorded at 60 MH_Z using TMS as internal reference.

2-Methyl-3-carbethoxyisoquinolinium iodide. To a soln of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10 g) in tetralin (300 ml), was added Pd-C (2 g; 10%), and the resulting suspension was heated under reflux for 6 hr, under N_2. After cooling, the charcoal was removed by filtration, the soln extracted with 2N HCl (3 × 100 ml) and the extracts combined and washed with ether. On basification with Na_2CO_3, the aqueous soln was re-extracted with ether (3 × 50 ml). After drying and evaporation, the combined ethereal extracts gave 2-methyl-3-carbethoxyisoquinoline as a pale yellow oil (8·85 g). Without further purification, the base was dissolved in acetone (20 ml) and MeI (10 ml) added. After standing overnight, pale yellow needles were obtained m.p. 162–163° (8·5 g; 72%) ν_{max} cm^{-1}, 1735 (C=O); $\lambda_{max}(\epsilon)$ nm, 241 (56,300) 277 (3,320) 341 (7,400); NMR (CD_3SOCD_3) ppm, 10·44 singlet [1] (C_1—*H*) 9·28 singlet [1] (C_4—*H*) 8·1–8·7 complex [4] (aromatics) 4·70 singlet [3] (N^+—CH_3) 4·56 quartet [2] $J = 7$ Hz (—OCH_2CH_3) 1·48 triplet [3] $J = 7$ Hz (—OCH_2CH_3). (Found: C, 45·45; H, 4·0; N, 4·25; I, 36·6. $C_{13}H_{14}NO_2I$ requires: C, 45·5; H, 4·1; N, 4·1; I, 37·0%.)

Condensation of aldehydes with ethyl 2-methyl-1,2-dihydroisoquinoline-3-carboxylate. To a soln of the crude 1,2-dihydroisoquinoline (ex borohydride reduction of the above methiodide (1·0 g)) in EtOH (20 ml) was added an equimolecular amount of the aldehyde. The resulting soln was heated with stirring in a N_2 atmosphere, and conc HCl (5 ml) was added dropwise. After 2 hr heating, the soln was left to cool overnight. The mixture was reduced to low bulk *in vacuo*, water (10 ml) added and the soln washed with ether (3 × 20 ml). The aqueous phase was again evaporated, and the residue dissolved in EtOH (5 ml). After adding a few drops of perchloric acid, the appropriate 4-substituted isoquinolinium salt slowly deposited (Tables 1 and 2).

The ketal (**10a**). A soln of **9a**[13] (0·90 g), *p*-toluenesulphonic acid (0·9 g) and ethylene glycol (2·0 ml) in dry benzene (50 ml) was heated under a Dean and Stark trap until no more water was liberated (about 4 hr). On cooling, the soln was washed with sat $NaHCO_3$aq and water, and then dried. Evaporation of the solvent yielded a pale yellow oil which slowly crystallised to give nearly colourless plates. Recrystallisation from light petroleum (60–80°)

Table 1. Physical data of products from the alkylation of **6**

	% Yield*	m.p.	Molecular Formula	Analysis Required C	H	N	Cl	Found C	H	N	Cl
R=C_6H_5	62	177–179°	$C_{20}H_{20}NO_6Cl$	59·2	5·0	3·45	8·7	59·5	5·3	3·6	8·4
R=3,4-$C_6H_3(OCH_3)$	56	159–161°	$C_{22}H_{24}NO_8Cl$	56·7	5·2	3·0	7·6	56·5	5·4	3·3	7·9
R=3,4-$C_6H_3(O_2CH_2)$	56	248–250°	$C_{21}H_{20}NO_8Cl$	56·0	4·7	3·1	7·9	56·4	4·2	3·4	7·6
R=$CO_2C_2H_5$	26	141–143°	$C_{17}H_{18}NO_8Cl$	50·8	5·0	3·5	8·8	50·5	4·5	4·1	9·2
R=$COCH_3$	47	155–157°	$C_{16}H_{18}NO_7Cl$	51·7	4·9	3·8	9·5	52·0	4·7	4·0	9·85

*Based on methiodide of ethyl isoquinoline-3-carboxylate

Table 2. Spectral data of products from the alkylation of **6**

	NMR–ppm						IR	UV
	C_1—H	CH_2 s	CH_3 Ns	CH_2 q	CH_3 t	Misc.	ν_{max} cm^{-1}	λ_{max} nm
R=C_6H_5	9·68	4·72	4·66	4·68	1·42		1785 (C=O) 1735 1635 (C=N$^+$)	237 (62,000) 282 (7,150) 342 (8,250)
R=3,4-$C_6H_3(OCH_3)_2$	9·74	4·66	4·66	4·68	1·48	3·94s (OCH_3)	1745 (aroms) 1635 (C=N$^+$)	237 (41,800) 344 (7,200)
R=3,4-$C_6H_3(O_2CH_2)$	9·70	4·74	4·68	4·70	1·50	5·96s (OCH_2O)	1780 (C=O) 1735 1630 (C=N$^+$)	238 (51,200) 344 (7,900)
R=$COOC_2H_5$	9·24	4·94	4·68	4·42	1·34	4·82q (CH_2) 1·60t (CH_3)	1740 (C=O) 1635 (C=N$^+$)	240 (61,300) 280 (4,150) 343 (10,000)
R=$COCH_3$	9·72	4·74	4·66	4·68	1·56	2·60 ($COCH_3$)	1730 (C=O) 1635 (C=N$^+$)	242 (45,300) 345 (8,600)

s = singlet; t = triplet; q = quartet; m = multiplet.

gave the required **10a** (0·92 g; 83%) m.p. 87°: NMR ($CDCl_3$) ppm, 7·1 complex [4] (aromatics) 3·9 complex [4] (—OCH_2CH_2O—) 4·2–2·0 complex [9] (aliphatics). (Found: C, 72·8; H, 7·6; N, 6·2. $C_{14}H_{17}NO_2$ requires: C, 72·7; H, 7·4; N, 6·1%.)

Dehydrogenation of ketal (**10a**). A soln of the ketal (500 mg) and anhyd NaOAc (200 mg) in EtOH (20 ml) was heated on a steam-bath, while I_2 (1·0 g), as a soln in EtOH, was slowly added. On cooling, the soln was saturated with SO_2 to remove excess I_2, and then concentrated to low bulk. Water (100 ml) was added, and the mixture was extracted with chloroform (3 × 20 ml). After drying and evaporation of the solvent, the combined extracts gave a yellow solid (220 mg) which was recrystallised from EtOH m.p. 205–210°; ν_{max} cm^{-1} 1640 (C=N$^+$) 1615 (C=C); λ_{max} nm 235, 342.

N-(*β-Cyanoethyl*)-3,4-*methylenedioxyphenylalanine*. 3,4-Methylenedioxyphenylalanine (3·65 g) was suspended in water (15 ml) and NaOH (0·70 g) added; the mixture was then vigorously stirred until complete soln was attained. Acrylonitrile (1·15 ml) was introduced, maintaining the temp below 20°. The soln was left stirring overnight at room temp, and then heated on a steam-bath for 2 hr. After cooling, the soln was neutralised to pH 7 with 2N HCl. The resultant solid was collected and recrystallised from water, giving the nitrile as white needles (3·76 g; 82%) m.p. 233–234°; ν_{max} cm^{-1} 3200–2400 (NH_2^+) 2250 (C≡N) 1585 (CO_2^-); NMR (CF_3COOH) ppm, 6·9 complex [3] (aromatics) 6·00 singlet [2] (—OCH_2O—) 4·05 multiplet [1] (—CH_2CH—) 2·8–3·9 complex [6] (3x—CH_2—). (Found: C, 59·75; H, 5·5; N, 10·7. $C_{13}H_{14}N_2O_4$ requires: C, 59·5; H, 5·4; N, 10·7%.)

N-(*β-Carbethoxyethyl*)-3,4-*methylenedioxyphenylalanine, ethyl ester*. N-(β-cyanoethyl)-3,4-methylenedioxyphenylalanine (2·94 g), dissolved in EtOH (120 ml) and conc H_2SO_4 (10 ml), was heated under reflux for 40 hr. After concentration *in vacuo* to approx 30 ml, ice-water was added and the soln was made alkaline with ammonia. The mixture was extracted with ether (3 × 25 ml) and the extracts dried. Evaporation of the solvent gave a pale-yellow oil (3·11 g; 82%); ν_{max} cm^{-1} 3360 (N—H) 1730 (C=O); NMR ($CDCl_3$) ppm, 6·7 complex [3] (aromatics) 5·90 singlet [2] (—OCH_2O—) 4·12 quartet [4] J = 7 Hz (2x—OCH_2CH_3) 3·4 multiplet [1] (—CH_2CHCO—) 2·1–3·0 complex [6] (3x—CH_2—) 1·96 singlet [1] (—N*H*—, disappears on deuteration) 1·22/1·18 two triplets [6] J = 7 Hz (2x—OCH_2CH_3).

Ethyl 2-(*β-carbethoxyethyl*)-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate*. The previously described diester (3·1 g) was suspended in water (20 ml) and conc HCl (1·0 ml) was added. Complete soln was obtained by vigorous shaking, and the pH was then adjusted to 4 with NaOHaq. After addition of formalin (9·0 ml; 37%), the soln was left at 32° for 72 hr. Then a further portion of conc HCl (0·70 ml) was added, and the mixture was heated on a steam-bath for ½ hr. After cooling, the aqueous soln was extracted with ether, and then made basic with ammonia. Extraction with ether and evaporation gave a yellow oil (2·28 g; 71%); ν_{max} cm^{-1} 1735 (C=O); λ_{max} nm 293; NMR ($CDCl_3$) ppm, 6·52/6·48 two singlets [2] (C_5—*H*, C_8—*H*) 5·86 singlet [2] (—OCH_2O—) 4·12 quartet [4] J = 7 Hz (2x—OCH_2CH_3) 3·6–3·9 complex [3] (ArCH_2N<, —CH_2CH<) 3·0 complex [4] (ArCH_2CH—, —CH_2CH_2CO—) 2·56 triplet [2] J = 7 Hz (>NCH_2CH_2—) 1·22/1·20 two triplets [6] J = 7 Hz (2x—OCH_2CH_3).

1,2,3,4,5,10,10a-*Hexahydro*-7,8-*methylenedioxypyrrolo*-[1,2-b]*isoquinoline*-1-*one* (**9b**). Na (80 mg) was added to "super-dry" EtOH (20 ml). When the reaction had ceased, dry benzene (100 ml) was introduced and the mixture heated on a steam-bath. After removal of the solvents, the ester (6 g) (from the previous reaction) in dry benzene (50 ml) was added and the mixture evaporated to dryness over a period of 3 hr. HCl (20% 150 ml) was then introduced and the soln heated to 100° for a further 3 hr. After cooling and extraction with ether, the soln was basified with Na_2CO_3. Re-extraction with CH_2Cl_2 and evaporation of the dried extracts afforded a pale yellow

solid (3·65 g, 92%); m.p. 176–178° (MeOH); ν_{max} cm^{-1}, 1750 (C=O); λ_{max} 294 nm; NMR ($CDCl_3$) ppm, 6·64, 6·56 two singlets [2] (aromatics) 5·9 singlet [2] (—OCH_2O—) 4·0 multiplet [1] (—CH_2CHCO—), 4·5 multiplet [2] (Ar.CH_2N) 2·2–3·0 complex [6] (3x CH_2—). This material rapidly darkened on standing and was characterized *via* its derivatives:

The ketone (1·09 g) was dissolved in aqueous EtOH (20 ml) and $NaBH_4$ (1·0 g) added in portions over 3 hr. Extraction with chloroform (3 × 25 ml) gave, after removal of the solvent, a colourless residue (0·91 g) which crystallized from EtOH to produce needles of **9b** m.p. 189–190°; λ_{max} cm^{-1}, 3200 (OH); λ_{max} (ϵ) nm, 292 (4,300). (Found: C, 66·95; H, 6·45; N, 6·1.. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%.)

Ketalisation of **9b**. The ketone (7·6 g) was dissolved in dry benzene (250 ml), together with ethylene glycol (10 ml) and *p*-toluenesulphonic acid (7·6 g). The mixture was then heated under a Dean and Stark trap, until free from water. After cooling, the soln was washed firstly with Na_2CO_3aq and then with water. The benzene soln was then dried and evaporated to give a pale yellow oil (2·08 g).

The crude ketal (0·2 g) was purified by eluting through a column of alumina (30 g) with 1:3 chloroform-benzene as solvent. The resultant oil then slowly crystallised to give buff-coloured plates m.p. 97–98°; λ_{max} (ϵ) nm, 293 (5,200); NMR ($CDCl_3$) ppm, 6·60/6·52 two singlets [2] (aromatics) 5·88 singlet [2] (—OCH_2O—) 3·9 complex [4] (—OCH_2-CH_2O—) 1·8–3·5 complex [9] (aliphatics). (Found: C, 64·5; H, 6·0; N, 4·95. $C_{15}H_{17}NO_4$ requires: C, 65·4; H, 6·2; N, 5·1%.)

The methiodide of the above ketal (**10b**) was prepared as buff-coloured blades (EtOH), m.p. 262–263°; λ_{max} (ϵ) nm, 293 (5,150). (Found: C, 46·3; H, 5·0; N, 3·3; I, 30·8. $C_{16}H_{20}NO_4I$ requires: C, 46·1; H, 4·8; N, 3·4; I, 30·4%.)

Dehydrogenation of the ketal (**10b**). The ketal (1·8 g) was dehydrogenated as previously described for **9a** to yield brown prisms (1·37 g; 32%) which recrystallised from EtOH to give **11b** as dark brown needles m.p. 212–213° (dec); ν_{max} cm^{-1} 1620 (C=N$^+$); λ_{max} (ϵ) nm 260 (99,000); NMR (DMSO) ppm, 9·8 singlet [1] (C_1—*H*), 8·3 singlet [1] (C_4—H), 7·85, 7·76 two singlets [2 × 1] (C_5—*H*, C_8—*H*), 6·4 singlet [2] (OCH_2O), 5·0 triplet J = 4H$_z$ [2] ($^+$NCH_2) 4·2 complex [4] (OCH_2CH_2O), 2·8 triplet J = 4H$_z$ [2] (CH_2C). (Found: C, 28·1; H, 2·3; N, 2·3; I, 58·0. $C_{15}H_{14}NO_4I_3$ requires: C, 27·8; H, 2·2; N, 2·15; I, 58·2%.)

On repetition of the above experiment using smaller amounts of I_2 and shorter reaction times (3 hr), a further periodide salt was isolated in similar yields (15–25%) which proved to be **13** as brown needles m.p. 170–171° (dec) (EtOH/acetone); ν_{max} cm^{-1} 1650 (C=N$^+$); λ_{max} (ϵ) nm 255 (19,900) 295 (21,700) 370 (20,300). (Found: C, 27·7; H, 2·6; N, 2·0; I, 58·4. $C_{15}H_{16}NO_4I_3$ requires: C, 27·5; H, 2·5; N, 2·1; I, 58·2%.)

Ethyl N-*carbethoxymethyl-β-aminopropionate*. N-β-cyanoethylglycine (82·4 g) was heated under reflux for 36 hr with a mixture of conc H_2SO_4 (100 ml) and EtOH (1 l). The soln was concentrated *in vacuo* to 200 ml and ice-water added. After basification with ammonia, the mixture was extracted with ether (3 × 50 ml). After being washed with water and dried, the combined ethereal extracts gave a colourless oil (90·4 g; 68%); ν_{max} cm^{-1} 3380 (N—H) 1735 (C=O); NMR (CCl_4) ppm, 4·24/4·18 two quartets [4] J = 7 Hz (2x—OCH_2CH$_3$) 3·32 singlet [2] (—NHCH_2CO) 2·3–3·1 complex [4] (NHCH_2CH_2—) 2·08 singlet [1] (—NH, disappears on deuteration) 1·34 triplet [6] J = 7 Hz (—OCH_2CH_3).

Ethyl N-*carbethoxy*-N-*carbethoxymethyl-β-aminopropionate*. The diester (90·4 g) described in the previous experiment was cooled to 10° and ethyl chloroformate (60·0 g) slowly added. The mixture was allowed to warm to room temp and left for 1 hr. $NaCO_3$ (25·0 g) in water (90 ml) was then added, and the mixture heated on a steam-bath for ½ hr. On cooling, ether (200 ml) was added and the etheral layer washed with 2N HCl (2 × 200 ml), and then water. On drying and evaporation a colourless oil was obtained (106·8 g; 88%); ν_{max} cm^{-1} 1740 (C=O) 1700 (NC=O).

1,4-*Dicarbethoxypyrrolidin*-3-*one*. The triester (106·8 g) described above, in benzene (100 ml) was slowly added to a heated soln of NaOEt (from Na 18·0 g) in benzene (300 ml), while the solvent was allowed to distil slowly from the reaction vessel. After all the triester had been added (about 3 hr) the heating was continued for a further 3 hr, until liberation of the EtOH produced in the reaction was complete. On cooling, AcOH (100 ml) was added and the organic phase washed with water. The benzene layer gave a yellow oil (80·2 g; 90%); ν_{max} cm^{-1} 1770, 1700 (C=O) after evaporation.

1-*Carbethoxypyrrolidin*-3-*one*. The β-ketoester (80·2 g) from the previous reaction was heated under reflux for 8 hr with AcOH (75·6 g) in water (600 ml). On cooling, the soln was made basic with 2N NaOH, and extracted with CH_2Cl_2 (5 × 50 ml). Evaporation of the organic extracts gave 1-carbethoxypyrrolidin-3-one as a pale yellow oil (48·9 g; 89%); ν_{max} cm^{-1} 1760 (C=O) 1700 (NC=O); NMR (CCl_4) ppm, 4·14 quartet [2] J = 7 Hz (—OCH_2-CH$_3$) 3·80 triplet [2] J = 7 Hz (—CH_2CH_2CO—) 3·70 singlet [2] (—NHCH_2CO) 2·56 triplet [2] J = 7 Hz (—CH_2CH_2NH—) 1·26 triplet [3] J = 7 Hz (—OCH$_2$-CH_3).

7-*Carbethoxy*-1,4-*dioxa*-7-*azaspiro*[4,4]*nonane*. 7-Carbethoxy-pyrrolidin-3-one (48·9 g), *p*-toluenesulphonyl chloride (1·0 g) and ethylene glycol (20 ml) were heated together under reflux in benzene (300 ml) for 6 hr, with a Dean-Stark adaptor fitted to trap the water produced. The soln was then washed with Na_2CO_3aq, and water. On drying and evaporating the benzene, a pale yellow oil (47·5 g; 76%); ν_{max} cm^{-1} 1700 (C=O); NMR (CCl_4) ppm, 4·24 quartet [2] J = 7 Hz (—OCH_2CH$_3$) 3·80 triplet [2] J = 8 Hz (—COH_2CH$_2$) 3·70 singlet [2] (—NCH_2CO—) 2·56 triplet [2] J = 8 Hz (—NCH_2CH$_2$—) 1·26 triplet [3] J = 7 Hz (—OCH$_2$CH_3), was formed, which was used for the next stage without further purification.

1,4-*Dioxa*-7-*azaspiro* [4,4] *nonane*. The amide (47·5 g) was heated overnight under reflux with KOH (37·5 g) in water (180 ml). After cooling, the mixture was extracted with CH_2Cl_2 (4 × 40 ml), and, after drying and evaporation of the solvent, the combined extracts gave a pale yellow oil. Vacuum distillation afforded a colourless oil (23·2 g; 76%) b.p.$_{12}$ 90–95° (Lit. [14]b.p.$_{0.4}$ 53°); ν_{max} cm^{-1} 3350 (N—H); NMR (CCl_4) ppm, 3·84 singlet [4] (—OCH_2CH_2-O—) 2·94 triplet [2] J = 7 Hz (—NHCH_2CH$_2$—) 2·74 singlet [2] (—CCH_2NH—) 1·88 singlet [1] (—NH, disappears on deuteration) 1·82 triplet [2] J = 7 Hz (—CCH_2CH$_2$—).

7-(o-*Carbomethoxybenzoyl*)-1,4-*dioxa*-7-*azaspiro* [4,4]-*nonane*. 1,4-Dioxa-7-azaspiro [4,4] nonane (23·2 g) and K_2CO_3 (13·5 g) were stored at 0° in water (300 ml) while methyl *o*-chloroformylbenzoate (36·0 g) in acetone (120 ml) was added dropwise over a period of 5 min. The soln was left overnight at room temp, and then extracted with

ether (3 × 50 ml). The combined ether extracts were washed with 2N HCl, and water. After drying, the solvent was evaporated to yield a pale yellow oil (42·9 g; 82%); ν_{max} cm^{-1} 1720 (C=O) 1635 (>NC=O).

N-(o-*Carbomethoxybenzoyl*)*pyrrolidin*-3-*one*. The preceeding ketal (14·5 g) and oxalic acid (12·6 g) were heated overnight under reflux in EtOH (100 ml) and water (200 ml). The soln was extracted with chloroform (3 × 50 ml), and the combined organic layers were washed with $NaHCO_3$aq and then water. On drying and evaporation, a colourless oil (8·72 g; 71%) remained which slowly crystallised on standing to give the required ketone m.p. 95–97° (lit.[14] m.p. 97–98°).

2,3-*Dihydro*-10-*hydroxypyrrolo*[1,2-b]*isoquinolin*-1,5-*dione*. The previously obtained ester (3·0 g) was heated under reflux in diphenylether (50 ml) for 20 min. On cooling, the soln was extracted with dilute NaOHaq (3 × 20 ml), and the combined aqueous layers were acidified.

The resultant green solid was collected, and recrystallised from EtOH to give **14** (1·96 g; 79%) m.p. 172–173° (Lit.[14] m.p. 175–176°) ν_{max} cm^{-1} 3600–3200 (O—H) 1695 (C=O) 1625 (>NC=O); λ_{max} (ϵ) nm 217 (28,200) 260 (6,100) 356 (6,800); NMR ($CDCl_3$) ppm, 8·6–7·5 complex [4] (aromatics) 4·38 triplet [2] J = 8 Hz (—COCH_2CH$_2$—) 2·92 triplet [2] J = 8 Hz (—CH$_2$CH_2N<). (Found: C, 66·4; H, 4·4; N, 6·3. Calc. for $C_{12}H_9NO_3$: C, 67·0; H, 4·2; N, 6·5%.)

Attempted reactions of 2,3-*dihydro*-10-*hydroxypyrrolo*-[1,2-b]*isoquinolin*-1,5-*dione*.

(i) The ketone (1·0 g) and *p*-toluenesulphonic acid (20 mg) was heated under reflux in benzene (50 ml) for 6 hr with ethylene glycol (5 ml). The mixture was cooled, and extracted with 2N NaOH (2 × 20 ml). Acidification of the combined aqueous layers gave unchanged starting material (0·94 g).

(ii) The ketone (1·0 g) was heated on a steam-bath for 6 hr with Ac_2O (or benzoyl chloride) (10 ml). On cooling, water (100 ml) was carefully added and the resultant solid collected, and recrystallised from EtOH to yield starting material (0·82 g).

(iii) The ketone (1·0 g) was heated on a steam-bath with acetyl chloride (2 ml) in pyridine (10 ml) for 6 hr. The mixture was poured into water, and acidified with 2N HCl to give starting material (0·98 g).

(iv) The ketone (1·0 g) was heated under reflux with LAH (1·0 g) for 6 hr in THF (50 ml). On cooling, saturated sodium potassium tartrate soln (20 ml) was carefully added, and the resultant clear soln decanted. The THF was removed *in vacuo*, benzene (30 ml) added, and the soln was extracted with 2N NaOH (2 × 20 ml). Acidification with HCl gave starting material (0·92 g).

7-(o-*Hydroxymethylbenzoyl*)-1,4-*dioxa*-7-*azaspiro*[4,4]-*nonane*. A mixture of the ester (5·0 g) and $NaBH_4$ (5·0 g) were stirred overnight at room temp in EtOH (150 ml). Water (500 ml) was added and the soln extracted with chloroform (3 × 50 ml). After drying and evaporation of the solvent, a colourless oil (2·80 g; 62%) was obtained, which was used in the next stage without further purification; ν_{max} cm^{-1} 3420 (O—H) 1615 (C=O).

7-(o-*Formylbenzoyl*)-1,4-*dioxa*-7-*azaspiro*[4,4]*nonane*. A mixture of the crude alcohol (2·80 g) and freshly prepared MnO_2 (15·0 g) in EtOH-free chloroform (150 g) was stirred overnight at room temp. The MnO_2 was removed by filtration and the solvent evaporated from the filtrate to yield a colourless oil (1·88 g; 68%); ν_{max} cm^{-1} 1705 (CH=O) 1620 (>NC=O).

2,3-*Dihydropyrrolo*[1,2-b]*isoquinolin*-1,5-*dione* (**15**). The above aldehyde (1·88 g) was dissolved in conc H_2SO_4 (20 ml), and the soln left overnight. The mixture was then poured onto ice-water, and the aqueous phase was extracted with chloroform (3 × 20 ml). On drying and evaporation of the solvent, a yellow solid (0·80 g; 56%) remained which recrystallised from EtOH to give pale-yellow plates m.p. 189–191° (lit.[14] m.p. 191–192°); ν_{max} cm^{-1} 1730 (C=O) 1650 (>NC=O); λ_{max} (ϵ) nm 250 (9,600) 335 (14,400); NMR ($CDCl_3$) ppm, 8·4 multiplet [1] (C$_6$—*H*)7·7 complex [3] (aromatics) 7·12 singlet [1] (C$_{10}$—H) 4·32 triplet [2] J = 6 Hz (—COCH_2CH$_2$—) 2·88 triplet [2] J = 7 Hz (—CH$_2$CH_2—N<). (Found: C, 72·4; H, 4·7; N, 7·2. Calc. for $C_{12}H_9NO_2$: C, 72·35; H, 4·55; N, 7·0%.)

Ketalisation of 2,3-*dihydropyrrolo*[1,2-b]*isoquinolin*-1,5-*dione*. A soln of the ketone (0·20 g), *p*-toluenesulphonic acid (0·10 g) and ethylene glycol (5·0 ml) were heated under reflux in dry benzene (100 ml) under a Dean and Stark trap. When no more water could be removed, the mixture was cooled, and washed with sat Na_2CO_3aq and water. Evaporation of the benzene yielded a pale-yellow oil, which was eluted through a column of alumina (30 g) with 1:1 benzene-chloroform mixture. This gave the ketal as a pale yellow oil (0·21 g; 86%) which slowly recrystallised to buff-coloured platelets m.p. 35–38°; ν_{max} cm^{-1} 1660, 1630, 1600 (>NC=O); λ_{max} (ϵ) nm, 226 (17,800) 249 (7,300) 291 (9,500) 325 (4,800) 338sh (3,500); NMR ($CDCl_3$) ppm, 8·5 multiplet [2] (C$_6$—*H*) 7·6 complex [3] (aromatics) 6·62 singlet [1] (C$_{10}$—*H*) 4·2 complex [6] (—OCH_2CH_2O—, —NCH_2CH$_2$—) 2·38 triplet [2] J = 7 Hz (—CCH_2CH$_2$). (Found: C, 69·1; H, 5·2; N, 5·7. $C_{14}H_{13}NO_3$ requires: C, 69·1; H, 5·4; N, 5·8%.)

Reduction of the above ketal. The ketal (250 mg) was dissolved in THF (150 ml) and LAH (0·50 g) was added. The suspension was heated for 2 hr and, after cooling, the excess LAH was destroyed with sat sodium potassium tartrate soln. The THF soln was decanted off and evaporated to low bulk *in vacuo*. The residue was dissolved in water (50 ml) and extracted with CH_2Cl_2 (3 × 25 ml). After drying and evaporation, the combined extracts yielded the amine **17** as an off-white solid (186 mg; 79%), which recrystallised from EtOH as white needles m.p. 112–116°; ν_{max} cm^{-1} 1645 (C=C); λ_{max} (ϵ) nm, 238 (6,300) 334 (6,900); (Found: C, 73·2; H, 6·7; N, 6·1. $C_{14}H_{15}NO_2$ requires: C, 73·4; H, 6·6; N, 6·1%.)

N-(*β-Carbethoxyethyl*)*isocarbostyril*-3-*carboxylic acid* (**19a**).

(a) Isocoumarin-3-carboxylic acid (0·2 g) was heated under reflux in EtOH (50 ml) for 6 hr, during which time ethyl *β*-aminopropionate (5 ml) was slowly added. The heating was continued for a further 10 hr, and the soln then concentrated to low bulk. Benzene (50 ml) was added and the soln extracted with sat Na_2CO_3aq (3 × 30 ml). After washing with benzene, the combined aqueous extracts were made acid with HCl and extracted with chloroform (3 × 30 ml). After drying and evaporation, the chloroform soln gave a white ppt (0·21 g; 69%). Recrystallisation from benzene gave the isocarbostyril as white needles m.p. 112–113°; ν_{max} cm^{-1} 3300–2500 (O—H) 1725 (C=O) 1630 (CON<); λ_{max} (ϵ) nm, 225 sh (14,800) 301 (7,800)

325 sh (6,000); (Found: C, 62·2; H, 5·2; N, 4·9. $C_{15}H_{15}NO_5$ requires: C, 62·3; H, 5·2; N, 4·8%.)

(b) Isocoumarin-3-carboxylic acid (7·75 g) in EtOH (100 ml) was stood for 7 days at room temp with ethyl β-aminopropionate (25 g). The EtOH was removed *in vacuo*, benzene (100 ml) added and the soln extracted with sat Na_2CO_3aq (3 × 50 ml). The combined aqueous extracts were washed with benzene and then acidified with dilute HCl. Extraction with chloroform (3 × 50 ml) and evaporation of the solvent gave 2-β-carbethoxyethylisocarbostyril-3-carboxylic acid (10·7 g; 91%.)

Ethyl N-(*β-carbethoxyethyl*) *isocarbostyril-3-carboxylate* (**19b**). The acid (2·46 g) was heated under reflux for 18 hr with conc HCl acid (30 ml) in EtOH (250 ml). The soln was reduced to 50 ml *in vacuo* and ice-water added. After basification with ammonia, the soln was extracted with CH_2Cl_2 (3 × 30 ml). The extracts were dried and evaporated to a yellow oil (2·25 g; 83%); ν_{max} cm^{-1} 1725 (CO_2Et) 1660 (CON<); NMR ($CDCl_3$) ppm, 8·4 multiplet [1] (C_8—*H*) 7·4–7·8 complex [3] (aromatics) 7·22 singlet [1] (C_4—*H*) 4·0–4·7 complex [6] (2x—OCH_2CH_3, —CH_2CH_2CO—) 2·94 triplet [2] $J = 7$ Hz (>NCH_2-CH_2—) 1·42/1·22 two triplets [6] $J = 7$ Hz (2x—OCH_2-CH_3).

Ethyl 1,5-*dioxa*-2,3-*dihydropyrrolo*[1,2-b]*isoquinoline*-2-*carboxylate*. A soln of NaOEt, made *in situ* from Na (0·4 g), was heated under reflux in benzene (250 ml) and EtOH (20 ml), while a benzene soln of ethyl N-(β-carbethoxyethyl)isocarbostyril-3-carboxylate (2·8 g) was added dropwise. The azeotropic benzene-ethanol mixture was allowed to distill slowly from the mixture. When all the EtOH had been removed, the soln was cooled and extracted with 2N NaOH (3 × 30 ml). After washing with benzene the aqueous extracts were acidified with HCl and the resulting pot extracted with CH_2Cl_2. On drying and evaporation, a brown solid (1·85 g; 77%) resulted which afforded the β-ketoester on recrystallisation from EtOH as pale brown plates m.p. 166–169°; ν_{max} cm^{-1} 1730, 1710 (C=O) 1660 (CON<); λ_{max} (ε) nm, 249 (11,500) 254 (12,700) 261 sh (10,100) 329 (19,200) 345 (20,300) 355 (17,000). (Found: C, 67·4; H, 4·8; N, 5·5. $C_{15}H_{13}NO_4$ requires: C, 66·4; H, 4·8; N, 5·2%.)

2,3-*Dihydropyrrolo* [1.2-b] *isoquinolin*-1,5-*dione* (**15**). A soln of the β-ketoester (1·85 g) in EtOH (100 ml) was heated under reflux with 6N HCl (100 ml) for 3 hr. The EtOH was evaporated *in vacuo*, and the aqueous soln was extracted with chloroform (3 × 50 ml). After drying and evaporation of the combined extracts, the residue was recrystallised from EtOH to give the required ketone as pale-yellow plates (1·26 g; 93%) m.p. 189–191° (Lit.[14] m.p. 191–192°). This material was identical in all respects (m.p. mixed m.p., IR, UV, NMR) with authentic 2,3-dihydropyrrolo[1,2-b]isoquinolin-1,5-dione as prepared by the previous method.

Attempted reaction of amine (**17**) The amine (1·0 g), stirring under N_2, was heated under reflux with pyruvic aldehyde (10 ml) in EtOH (50 ml) while 6N HCl (10 ml) was added dropwise. The heating was then continued for 3 hr. The EtOH was removed *in vacuo*, and the aqueous soln was washed with ether (3 × 20 ml). The aqueous phase was then evaporated to dryness *in vacuo*, until all excess HCl had been removed. The residue was taken up in EtOH (10 ml), and perchloric acid (1·0 ml) added. The resultant solid was collected and recrystallised to give the quaternary salt (11a) as buff coloured needles (540 mg; 38%) m.p. 222–224°; ν_{max} cm^{-1} 1635 (C=N^+); NMR (CD_3SOCD_3) ppm, 10·00 singlet [1] (C_5—*H*) 8·74 singlet [1] (C_{10}—*H*) 8·6–8·0 complex [4] (aromatics) 5·06 triplet [2] $J = 7$ Hz (—CH_2CH_2—N^+) 4·3 complex [4] (—OCH_2-CH_2O—) 2·80 triplet [2] $J = 7$ Hz (—CCH_2CH_2—). (Found: C, 51·6; H, 4·5; N, 4·3; Cl, 11·0. $C_{14}H_{14}NO_6Cl$ requires: C, 51·3; H, 4·3; N, 4·3; Cl, 10·8%.)

Anhydride (**20**). 4-Carbethoxyisocoumarin-3-carboxylic acid (0·50 g) was heated under reflux with EtOH (20 ml) for 18 hr, ethyl β-aminopropionate (5 ml) being added very slowly over the first 6 hr. The EtOH was removed *in vacuo*, benzene (50 ml) added and the soln was extracted with sat Na_2CO_3aq (3 × 20 ml). After being washed with benzene, the combined aqueous extracts were acidified with dil HCl and then extracted with chloroform (3 × 30 ml). Drying and evaporation of the chloroform gave a pale-yellow oil. The product was heated with a small volume of benzene, whereupon the yellow colour intensified, and upon cooling the anhydride was deposited as yellow needles (0·30 g; 50%) m.p. 151–153°; ν_{max} cm^{-1} 1860, 1800, 1735, 1670 (C=O); λ_{max} (ε) nm, 214 (36,700) 299 (11,200). (Found: C, 60·7; H, 4·1; N, 4·6. $C_{16}H_{13}NO_6$ requires: C, 60·95; H, 4·3; N, 4·4%.)

Diethyl 2-(*β-carbethoxyethyl*) *isocarbostyril*-3,4-*dicarboxylate* (**21**). The anhydride (1·5 g) was dissolved in EtOH (250 ml) and the soln heated under reflux with conc H_2SO_4 (30 ml) for 72 hr. The soln was concentrated to low bulk, the residue dissolved in benzene, and the soln washed with sat Na_2CO_3aq and water. Evaporation of the benzene solution gave a pale-yellow oil (1·54 g; 84%) which was used in the next stage without further purification.

Diethyl 1,5-*dioxo*-2,3-*dihydropyrrolo* [1,2-b] *isoquinoline*-2,10-*dicarboxylate* (**22**). A soln of **21** (1·33 g) and NaOEt (from 0·16 g Na) in dry benzene (200 ml) were heated under reflux for 6 hr during which the azeotropic mixture of benzene and EtOH was slowly distilled. On cooling, the mixture was extracted with 2N NaOH (3 × 50 ml), washed with benzene, and the aqueous extracts rendered acid with 2N HCl. After chloroform extraction and drying, a white semi-solid (0·37 g; 32%) resulted on evaporation. Recrystallisation from EtOH gave the β-ketoester as white platelets m.p. 196–198°; ν_{max} cm^{-1} 3260 (O—H) 1735, 1720 (C=O) 1665 (CON<); λ_{max} (ε) nm, 214 (25,600) 256 sh (8,500) 332 sh (14,900) 347 (16,600) 356 (14,000); NMR ($CDCl_3$) ppm, 9·2 broad absorption [1] (—O*H*, disappears on deuteration) 8·4 multiplet [1] (C_8—*H*) 7·8–7·4 complex [3] (aromatics) 4·68 singlet [2] (—C—CH_2—N<) 4·46/4·34 two quartets [4] $J = 7$ Hz (—OCH_2CH_3) 1·46/1·38 two triplets [6] $J = 7$ Hz (—OCH_2CH_3). (Found: C, 63·0; H, 5·1; N, 3·95. $C_{18}H_{17}NO_6$ requires: C, 63·0; H, 5·0; N, 4·1%.)

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POLYSTYRENE WASTE IN THE SEVERN ESTUARY

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Polystyrene Waste in the Severn Estuary

Attention has been drawn recently to the widespread occurrence of polystyrene spherules (mean diameter 1 mm) in the coastal waters of southern New England, both in the water and in the intestines of eight species of teleost fish (Carpenter *et al.*, 1972). Similar spherules have been found in mud and sand samples from the southern shore of the Severn Estuary between Minehead and Sharpness, and at low water mark at Steart Flats (Bridgwater Bay) many polychaete worms of the species *Sabellaria alveolata* have constructed dwelling tubes almost entirely from such polystyrene spherules (personal communication: C. Little & C. R. Boyden, University of Bristol).

During the past winter (1972-1973) we have found the same type of polystyrene spherules among the stomach contents of 0+ and 1+ year class flounders (*Platichthys flesus*) caught on the cooling water intake screens of the nuclear power station at Oldbury-on-Severn. Some very young flounders (2-5 cm) had as many as thirty spherules each in their intestines.

From these observations it is clear that quantities of polystyrene spherules are being deposited in the Severn Estuary. Furthermore, irregular-shaped pieces of polystyrene, up to 3 g in weight and varying in colour from yellow to white, are a very common component of the 'trash' collected from the intake screens of the power stations at Hinkley Point, Oldbury-on-Severn and Berkely. Although the amounts vary daily, as many as a hundred pieces occur in one 24 h sample at Oldbury. Frequently this material is accompanied by pieces of paraffin wax of approximately the same size, though not necessarily in the same amounts. It is interesting that we have retrieved similar combinations of polystyrene and paraffin wax from several beaches along the North Devon coast, indicating the extensive distribution of these substances.

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ECOLOGICAL IMPLICATIONS OF HEAVY METALS IN FISH FROM THE SEVERN ESTUARY

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Ecological Implications of Heavy Metal in Fish from the Severn Estuary

Tissues and organs of the flounder collected from the Severn at Oldbury, in the course of a year long survey, have been analysed for lead, cadmium and zinc. Differences have been noted in the level of zinc deposition in the various age groups of this teleost, particularly in autumn and summer. In an attempt to explain these results, the feeding habits of the flounder have been studied and heavy metal analyses conducted on some of its principal foodstuffs and related animals.

Recent reports (Butterworth *et al.*, 1972; Nickless *et al.*, 1972; Peden *et al.*, 1973) have recorded relatively high levels of lead, cadmium and zinc in the tissues of several vertebrate and invertebrate species from the Bristol Channel and Severn estuary. Furthermore, the concentrations of these elements in the waters of this area have been shown to be much higher than in the open sea (Abdullah *et al.*, 1972; Preston *et al.*, 1972).

In attempting to assess the ecological significance of the heavy metal burden in the tissues of certain key estuarine species, analyses of lead, cadmium and zinc have been made on fish collected from the intake screens of the Oldbury Nuclear Power Station, located in the middle reaches of the Severn estuary. Species have been selected which differ in their migratory patterns, feeding habits and life span in the hope that it might be possible to relate heavy metal levels to these and other aspects of their biology. In view of the significant part that the shrimp (*Crangon vulgaris*) plays in the food chain of many estuarine teleosts, similar determinations have been made on this species, collected from both Oldbury and Milford Haven.

Materials and Methods

The majority of the species used in this study were obtained in the course of regular sampling from the intake screens of the nuclear power station at Oldbury-on-Severn, where the cooling water is drawn from a tidal reservoir built out over the intertidal flats immediately in front of the station.

In the course of the survey, over 1,250 flounders (*Platichthyes flesus*) were examined in collections made during October, 1972 and in February and June, 1973. In addition to recording the lengths and weights of individual fish, gut analyses were made on representative specimens of various size groups. The approximate age composition of selected length classes was ascertained by otolith examination combined with analysis of length-frequency distributions.

In addition to the flounder, heavy metal determinations were also made on the sand goby (*Pomatoschistus minutus*) and the sea snail (*Liparis liparis*) both of which occurred in considerable numbers in the power station samples. A limited number of gut analyses were also carried out on the latter species. Specimens of the anadromous river lamprey (*Lampetra fluviatilis*) were obtained in the course of their autumn and winter spawning migration through the Severn estuary, and samples of the nonmigratory and nonparasitic brook lamprey (*Lampetra planeri*) came from the river Honddu in Breconshire and the river Chew in Somerset.

Animal tissues and organs were dried at 105°C to constant weight (normally 24 h). Samples (approximately 1 g) were weighed accurately and digested in a mixture of hot perchloric acid (6 ml) and nitric acid (2·5 ml), both of Aristar grade, until a clear colourless solution was obtained (20 min at 100°C). The cold solution was then diluted to 25 ml with deionized water and analyzed directly using an Hilger-Watt Atomspek atomic absorption spectrophotometer. In each case, two blank determinations were conducted.

Standard readings were obtained by treating an aliquot of a solution containing known concentrations of metals in exactly the same manner as for the organic material. After acid treatment, the solution was made up to 25 ml with deionized water and analysed directly. Results were checked against analyses of the so-called 'standard kale', for which concensus readings were obtained (Bowen, 1967). In addition, some duplicate analyses were conducted at the laboratory of the Government Chemist, London; again, there was good correlation with our results.

TABLE 1

Lead, cadmium and zinc levels in the tissues of whole flounders (*Platichthyes flesus*) of different length and age classes.

Length (cm) and age classes	*Mean concentrations (ppm) dry tissue ± S.D. Lead			Cadmium			Zinc		
	Oct. 72	Feb. 73	June 73	Oct. 72	Feb. 73	June 73	Oct. 72	Feb. 73	June 73
7–9 (0+)**	13·9±1·1		19·7±1·3	3·9±0·5		3·4±0·4	143·8±2·8		173·1±1·4
14–17 (1+)	23·2±2·3	16·5±1·3	22·9±1·3	4·2±0·8	5·2±0·5	4·2±0·4	110·1±1·5	139·4±0·8	156·3±1·4
18 (2+,3+)	18·7±1·3	27·4±1·1	21·6±1·6	4·0±0·5	5·4±0·2	4·1±0·4	102·2±1·6	144·9±1·3	124·7±1·0
20 (3+,4+)	15·7±1·4	25·1±0·9	24·5±1·0	3·9±0·7	4·8±0·3	4·2±0·4	91·4±1·8	132·8±0·6	124·8±2·5
27–29 (5+)	22·4±1·1	27·4±1·1	29·2±1·1	5·2±1·0	7·3±0·7	5·1±0·8	76·3±1·3	175·6±1·3	147·5±1·0

* Results based on twenty analyses for each group. ** Not represented in the February sample.

Results

For comparative purposes, heavy metal concentrations have been expressed (Tables 1 and 2) as ppm dry weight based on digests of whole animals, but these concentrations may vary widely in different tissues. Thus, detailed analyses of different tissues or organs in the flounder have shown that lead muscle levels rarely exceed 20% of the values recorded for liver, heart or kidney tissue (approximately 20–30 ppm) and the highest concentrations were observed in the brain (38·5–43·6 ppm). For cadmium, muscle values were again relatively low, varying from 2–11% of those observed in the liver or kidney (21·2–27·5 ppm). Maximum zinc concentrations occurred in kidney tissue (300–420 ppm) and these levels were about four times as high as in liver, heart or brain and five times greater than the muscle concentrations.

In general, the highest zinc concentrations were those observed in the flounder, and, unlike the lead or cadmium levels, the concentrations of this element showed distinct seasonal and age variation (Table 1). Thus, both in autumn and summer samples, the highest zinc levels were recorded for the smallest flounders assigned to the 0+ year class and, in the remaining groups, there was a consistent decrease in zinc levels with increasing age and length. On the other hand, in the February samples (where the 0+ age class was not represented), the zinc values were higher than in autumn or summer and remained relatively constant over all length and age groups, apart from a higher value in the largest specimens. It is perhaps significant that the same length class in the June sample shows a similar departure from the otherwise downward trend of zinc levels with increasing length and age.

Neither the lead nor cadmium concentrations show a consistent decrease with increasing length or age and, indeed in the majority of cases, the largest flounders tend to exhibit the maximum levels of both elements. Furthermore, while the cadmium levels in the Oldbury fish are similar to those reported for flounders from Hinckley Point in the Bristol Channel (when recalculated in terms of dry weight), the zinc analyses from the latter area are much lower.

As in the Ythan estuary (Healey, 1971), the goby is an autumn and winter resident at Oldbury, weekly samples showing a more or less consistent increase in numbers from July onwards, reaching a peak in mid-winter and declining again in the early spring. In this species, lead and cadmium levels are of the same order as those of the flounder, but the zinc concentrations are distinctly lower and comparable only with those of the largest flounders in the sample of October, 1972 (Table 2).

The most significant feature of the heavy metal determinations carried out on the sea snail (Table 2) are in the cadmium levels, which are from four to five times higher than those observed in the sand goby and three to four times as high as in the flounder. On the other hand, lead levels were similar to those of the latter species, but rather higher than in the goby. Zinc figures are of the same order as many of the flounder samples and show a tendency to be somewhat reduced in the larger specimens.

In the case of all three elements, the concentrations recorded for the Severn river lamprey are very much below those of the three teleost species, but it is note-

TABLE 2

Levels of lead, cadmium and zinc in some estuarine and freshwater species.

Species	Location	No. of analyses	Mean concentrations (ppm) dry weight ± S.D. Lead	Cadmium	Zinc
Sand goby (*Pomatoschistus minutus*)*	Oldbury-on-Severn	20	17·6±0·9	3·2±0·5	75·6±2·0
Sea snail (*Liparis liparis*)*					
2–4 cm	Oldbury-on-Severn	10	29·9±1·2	13·7±0·5	107·9±1·5
5–9 cm	Oldbury-on-Severn	10	25·8±1·6	16·8±0·9	86·5±3·2
River lamprey (*Lampetra fluviatilis*)**	Oldbury-on-Severn	6	6·0±0·7	0·5±0·3	47·1±1·0
Brook lamprey (*Lampetra planeri*)**					
Adults	River Honddu	10	12·0±1·13	0·75±0·3	117·0±3·3
Ammocoetes	River Honddu	20	8·8±1·08	0·23±0·2	93·6±3·6
Ammocoetes	River Chew	10	8·6±1·0	1·25±0·3	199·3±1·0
Shrimp (*Crangon vulgaris*)*	Oldbury-on-Severn	10	34·0±1·0	124·8±1·5	125·9±1·1
	Milford Haven	10	55·6±1·6	4·9±0·6	101·0±1·0

* Collected during the period July 1972–February 1973. ** Collected during the period November 1972–April 1973.

worthy that the zinc values for both the larval and adult stages of the purely freshwater species, *Lampetra planeri*, are in general as high as those observed in some of the flounder samples from the estuary of the Severn. Cadmium concentrations are again very low, but the lead values tend to be somewhat higher than in the adult of the river lamprey.

Relatively high zinc levels were found in shrimps from both Milford Haven and Oldbury, and lead concentrations from both sites were generally rather higher than in Severn teleosts. The most significant feature of these analyses, however, is the high cadmium levels observed in the Oldbury shrimp samples.

Discussion

Without a much more detailed study of the biology of the flounder population of the Severn estuary, it is difficult to advance more than a tentative explanation of the observed seasonal and age variations in zinc concentrations. As can be judged from the power station samples, the relative abundance of the Oldbury flounders has followed a broadly biphasic pattern, with maximum numbers in summer falling to minimum levels in October (Hardisty & Huggins, unpublished observations). A second peak was reached at the beginning of January, 1973. These changes may well reflect seasonal movements in and out of the Oldbury region of the estuary which could differentially affect the older animals. Since there is evidence that ingested zinc may be excreted by both marine vertebrates and invertebrates (Skidmore, 1964; Bryan, 1968), the varying patterns of zinc accumulation might well reflect the varying periods which flounders of different age groups have spent within areas of higher or lower zinc concentrations.

The general tendency for zinc levels to decrease with age and length which was observed in the October and June samples is probably based on metabolic factors. The absence of this trend in the February sample and the uniformly higher values observed at this time, could be attributable, either to a change of diet, to differences in feeding intensity, or to movements into the area from other regions. Gut analyses indicate that the diet of the youngest flounders appears to be relatively constant throughout the year, consisting primarily of polychaetes, but there is considerable seasonal variation in the food intake of larger fish. Thus, in October, 1972 the gut contents of flounders of the 1+ age class or above showed the remains of gammarids, shrimps and gobies, but in early spring the shrimp was the dominant food organism, despite the fact that shrimps are said to be less numerous in the estuary at this time of the year (Lloyd & Yonge, 1947). Furthermore, it has been observed that the major food organism of the larger flounders in June, 1973 was the crustacean, *Macome baltica*, at a time when the shrimp was very abundant in the Oldbury area. In fact, very few individuals revealed the remains of shrimps in their gut contents during this period.

Bearing in mind that the goby population consists of only two age classes, the rate of accumulation of lead or cadmium appears to be of a similar order to that of flounders of comparable age, although zinc concentrations were considerably lower. For these reasons, it seems unlikely that the goby could be a significant factor in the heavy metal burden of the flounder, but the shrimp and other crustaceans may well be important factors. The contrast between the cadmium concentration of the sea snail and the goby is of special interest, suggesting that in spite of the apparent ecological parallels there may be basic differences in the diet of the two species. Gut analyses of the Oldbury sea snails indicate that the shrimp is an important element of the food of at least the larger animals. Thus, of 50 individuals examined, 45% of the guts contained mainly shrimps, while in 16% of cases they were the sole component. No gut analyses have been carried out on the Severn gobies, but detailed studies on this species in the Ythan estuary (Healey, 1971) have shown that the amphipod, *Corophium volutator* is the major constituent of the diet and that unlike the Severn sea snail, the shrimp is much less important. In this connection therefore, the exceptionally high cadmium concentrations of the Oldbury shrimps is highly significant.

The anadromous river lamprey, *Lampetra fluviatilis*, after a freshwater larval stage of about four and a half years, undergoes metamorphosis from the ammocoete and enters the estuary when about five years. For a further period of about one and a half years, the adult lamprey feeds parasitically on the blood and muscle tissues of teleost host species (Hardisty & Potter, 1971), probably within the area of the Bristol Channel, before re-entering the estuary on its spawning migration. It might therefore be anticipated that the heavy metal figures for this species would reflect the levels prevalent in the muscle and body fluids of host fishes within its feeding area. In fact, figures for all three elements are lower than for any other of the vertebrates studied; a circumstance that may partly be related to the comparatively low levels of heavy metals in the muscle tissue and blood on which these animals feed.

The figures for brook lampreys are particularly interesting in view of the fact that this species is entirely confined to freshwater and feeds only during the larval stage when the principal component of its diet is diatoms (Hardisty & Huggins, 1970). Thus, zinc values for ammocoetes of this species from the river Honddu in Breconshire are more than twice as high as in the Severn river lamprey, and specimens from the river Chew (arising in the Mendip Hills) had concentrations more than four times higher than those of the anadromous form (Table 2). These observations emphasize the need for caution when interpreting heavy metal concentrations without adequate information on background levels.

Clearly, at this stage, it is impossible to comment on the possible biological effects of heavy metal concentrations of the order of those observed in these estuarine fish species. The view has been expressed that in the area of the Bristol Channel, the deterioration in the variety of fish species has been greater than in any other region of the British coasts (Clark, 1971), although a more optimistic interpretation has been made on the basis of comparisons of growth in river lampreys from this area (Hardisty & Huggins, 1973). Furthermore, although no quantitative assessments are possible, comparisons of our fish samples from Oldbury intake screens with the faunal lists compiled by Lloyd (1940) for the same region, provide no evidence of deterioration in species variety over the last 30 years; and it is evident

that the Severn estuary still remains a satisfactory nursery ground for the juvenile stages of a number of marine teleosts as well as providing a migratory route for anadromous species.

The authors wish to express their gratitude to the CEGB for their co-operation in making this study possible, to many local fishermen, and to Dr Raymond Ward of the Government Chemist Laboratory, London for undertaking to duplicate some of our analyses.

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DIETARY HABITS AND HEAVY METAL CONCENTRATIONS IN FISH FROM THE SEVERN ESTUARY AND BRISTOL CHANNEL

(Marine Pollution Bulletin, 1974, 5(4), 61)

may, however, give us a feeling for the atmospheric lifetime of this type of material.

The most critical factor in determining man's impact on the hydrocarbon content in both the atmosphere and the ocean in non-urban areas is the ability to differentiate between the natural and man-made hydrocarbons actually present in these areas. As yet, this has been almost impossible to accomplish. There have been some indications that the heavier hydrocarbons collected in Bermuda have a petroleum source. This tentative assignment is based on: 1) the presence of an unresolved complex mixture of hydrocarbons; 2) the presence of the isoprenoid hydrocarbon, phytane; and 3) an approximate one to one ratio of odd and even chain *n*-alkanes, as measured by gas-liquid chromatography after isolation of the hydrocarbons by preparative thin-layer chromatography (Farrington *et al.*, 1973). It has been suggested that these three criteria indicate the possible presence of material with a petroleum source (NOAA, 1972). With this possible indication of a non-natural source in northern hemispheric marine air samples, a comparison of the heavier hydrocarbon distribution in both remote southern and northern hemisphere locations would be most desirable, since man's estimated northern hemispheric 'long-lived' hydrocarbon production (45 M tons/year) is almost 10 times the estimated southern hemispheric production (5 M tons/year).

Deposition in the Oceans

The question of the deposition rate of these atmospheric hydrocarbons into the ocean is even more difficult to answer at present. There is virtually no information on hydrocarbon concentrations in precipitation in remote marine areas. We do not have a sound basis for making estimates either of dry fallout of hydrocarbons present on atmospheric particles, or of direct gas exchange of any but the very lightest hydrocarbons between the ocean and the atmosphere. It seems likely that a considerable fraction of the 'long-lived' gaseous hydrocarbons found in the atmosphere in remote areas is not deposited on the earth's surface but ultimately undergoes atmospheric conversion reactions to oxygenated species. While these oxygenated organics are probably removed relatively rapidly from the atmosphere, they would no longer be hydrocarbons and would not contribute to the hydrocarbon concentrations found in the sea. Accurate estimates for the atmospheric input of hydrocarbons to the ocean surface must await direct measurements of these substances in rain and particulate matter dry fallout in the marine atmosphere. Studies of both the extent of gaseous exchange of heavier hydrocarbons across the air/sea interface and the reaction kinetics of these substances in the atmosphere will also be necessary before we can properly evaluate atmospheric transport to, and deposition of hydrocarbons in, the oceans.

We greatly appreciate the very helpful comments and information supplied by Dr R. A. Rasmussen. This work was supported in part by the National Science Foundation Office of the International Decade of Ocean Exploration under Grant GX-33777.

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Dietary Habits and Heavy Metal Concentrations in Fish from the Severn Estuary and Bristol Channel

Comparisons of the rates of growth, feeding habits and heavy metal levels of flounders from Barnstaple and Oldbury-on-Severn have shown that at all ages the fish from the North Devon coast are larger than those from the middle Severn estuary and that there are marked differences in diet. These differences in diet may contribute to the much higher zinc levels of the Barnstaple flounder samples.

In the six other fish species which have been examined, there is a distinct correlation between the cadmium concentrations of the tissues and the proportion of crustaceans in the diet. Lead concentrations appear to follow a similar trend, but no relationship could be detected between diet and tissue zinc levels.

In a recent communication (Hardisty *et al.*, 1974), we attempted to relate feeding behaviour and heavy metal

levels in the tissues of flounders, *Platichthyes flesus*, from the middle Seven estuary. Information on environmental heavy metal levels has indicated lower concentrations in the waters of the southern and western coastal regions of the Bristol Channel compared with regions above the Avonmouth industrial complex (Adhullah *et al.*, 1972: Preston *et al.*, 1972) and for this reason comparisons have now been made with flounders from the North Devon Coast.

Possible relationships between tissue heavy metal levels and diet have been further examined by extending our previous observations to cover a number of species, showing considerable difference in feeding habits.

Materials and Methods

At Barnstaple, flounders were obtained by trawling during July 1973. Flounders and the other six teleost species referred to in this paper were also collected from the intake screens of the Oldbury-on-Severn nuclear power station during the same month. Heavy metal analyses were conducted as previously described (Hardisty *et al.*, 1974) and age determinations were made by the method of otolith examination.

Results and Discussion

In the summer of 1973 flounders of the 6+ age class or older were common in the North Devon samples, but at Oldbury fish older than the 5+ age class were rarely observed. Moreover, at all ages the weights and lengths of the Barnstaple flounders are significantly greater than those of the fish from the estuary (Fig. 1a and b). On the other hand, these differences between the two populations are already established in the youngest 0+ age class and thereafter the rates of growth are very similar in both groups. The reasons for the apparently much greater initial growth rate of the North Devon flounders during the first year after spawning are not clear, but it is possible that the time of spawning may differ in the two populations. Furthermore, even if the rates of growth at the two sites were to differ this might be obscured by movement to and from the estuary and the Channel region

While lead, and more especially, cadmium concentrations are significantly lower in the Barnstaple samples (Table 1), surprisingly, the zinc levels are considerably higher. Although it is possible that these high zinc levels might be a result of local 'run off' the possibility that a dietary factor may be involved cannot be discounted. Analyses of the stomach contents of the Barnstaple fish show 87% contained the bivalve, *Macoma baltica*, and analyses of the tissues of this organism have produced zinc concentrations as high as 800 ppm dry weight, whereas cadmium and lead levels were relatively low. At Oldbury, on the other hand, *M. baltica* is only of minor significance in the diet of estuarine flounders, being represented in 30% of the oldest age class and in only 4% of the 2+ to 4+ age classes. In the latter, the principal dietary organisms were shrimps, *Crangon vulgaris*, (75%), gobies, *Gobius minutus* (7%) and gammarids (3%).

In an earlier communication (Hardisty *et al.*, 1974) we have commented on the high cadmium levels observed in shrimps and other Crustacea in the Oldbury

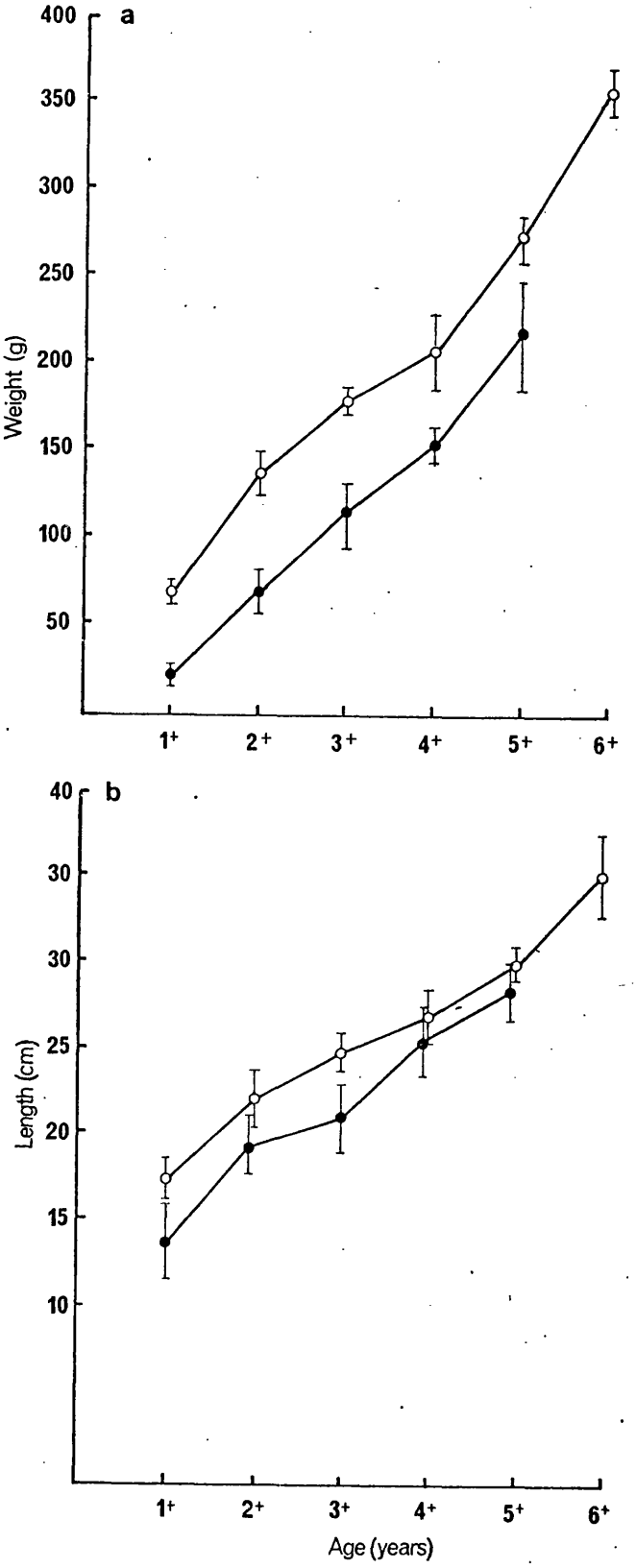

Fig. 1 Flounders from Oldbury (●) and Barnstaple Bay (○): (a) relationship between weight and age; (b) relationship between length and age.

region and suggested that this is a major factor responsible for the high cadmium concentrations that were observed in the sea snails, *Liparis liparis*, of this area. This is supported by the results of heavy metal analyses and by the gut contents of other teleost species, differing widely in their dietary preferences (Table 2).

TABLE 1

Comparison of heavy metal concentrations in flounders from Barnstaple Bay and Oldbury-on-Severn.

Locality	Element	Concentration present (ppm dry weight ± S.D.) in age group 2+	3+	4+	5+
Barnstaple Bay	Zn	224·5±2·81	209·4±1·63	200·2±5·52	195·2±5·54
	Cd	1·1±0·32	1·4±0·52	1·6±0·30	1·7±0·28
	Pb	14·1±1·24	16·0±1·24	18·0±0·71	19·1±1·21
Oldbury-on-Severn	Zn	125·2±1·00	128·0±4·01	128·6±2·03	140·0±1·04
	Cd	4·0±0·43	4·5±0·52	5·1±0·51	5·2±0·62
	Pb	20·5±1·45	24·0±1·58	26·2±1·00	28·2±1·21

TABLE 2

Crustacean intake and heavy metal concentrations in teleost species from Oldbury-on-Severn (July 1973).

Species	Number analysed*	% Crustacea in diet	Metal conc. (ppm/dry weight ± S.D.) in whole fish Zn	Cd	Pb
Sea snail, *Liparis liparis*	150	100	86·5±3·19	16·8±0·87	25·8±1·58
Bearded rockling, *Ciliata mustela*	20	90	180·2±3·42	8·1±2·27	22·0±0·72
Poor cod, *Trisopterus minutus*	100	80	158·1±1·58	8·5±1·23	20·0±0·29
Flounder, *Platichthyes flesus*	250	71	132·8±0·55	5·6±0·29	25·1±0·87
Whiting, *Merlangus merlangus*	337	70	124·8±0·51	6·2±0·19	24·0±0·98
Grey mullet, *Liza ramada*	100	15	120·0±0·23	3·0±1·20	18·8±1·57
Sand goby, *Gobius minutus*	20	10	75·6±2·01	3·2±0·53	17·6±0·86

*Analyses refer to fish of 1+ age group and above in all cases.

Although in those species which feed predominantly on crustaceans the shrimp is the major component of the gut contents, gammarids and mysids generally occur in much smaller numbers; in Table 2, therefore, these groups of organisms have been combined and expressed as percentages of the diet.

The lowest cadmium concentrations have been observed in the grey mullet, *Liza ramada*, and sand goby, *Gobius minutes*; in both species the gut contents contain only small numbers of crustaceans (15 and 10% respectively). On the other hand, maximum cadmium levers were recorded for the sea snail, in which crustaceans and the shrimp, in particular, form the sole constituent of the diet. Relatively high cadmium levels have also been found in the bearded rockling, *Ciliata mustela*, and the poor cod, *Trisopterus luscus*, in which crustaceans contribute 90% and 80% of the total diet.

Differences in the species concentrations of lead, while not as marked as in the case of cadmium, nevertheless show similar trends with minimum levels of 18·8 ppm in grey mullet and 17·6 ppm in the sand goby, compared with general levels of between 20–26 ppm in those species where crustaceans predominate in the diet. Zinc concentrations on the other hand show no obvious correlations with feeding habits, but it is interesting to find that markedly low levels have been recorded for sea snails and gobies, although the former species feeds entirely on crustaceans, which in the latter these organisms constitute only a very small element in their diet. In this connection it must be borne in mind that both species are small forms with a life cycle restricted to about two years only; and indeed the analyses refer in the majority of cases to animals of the 1+ age class, whereas in the other species studied specimens have been of more advanced age groups. Assuming that the zinc concentrations represent a dynamic balance between zinc uptake and excretion, it may well be that in areas such as the Severn estuary with high environmental zinc levels, tissue concentrations will generally tend to increase with the age of the fish.

Conclusions

Until more is known of the biology of the flounder in the area of the Bristol Channel and the estuary, particularly in relation to time of spawning and the movements of populations to and from the estuarine regions, it is impossible to do more than speculate as to the factors which may be responsible for the marked differences in body size between the populations from the North Devon coast and those of the middle estuary. However, in view of the similarities in growth rates beyond the first year or so of the life cycle, it seems unlikely that such difference could be attributed to the significantly greater concentrations of cadmium and lead in the tissues of the Oldbury flounders, although it is possible that conditions for the growth of the young of the year could be much less favourable within the estuarine region.

The observations that have been made on the relation between diet and lead and cadmium concentrations in several teleost species, point to the need for much more detailed studies of the circulation of heavy metals within the estuarine ecosystem, and in particular for further studies on the heavy metal levels within the main groups of food organisms.

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CARAPANAUBINE: AN OXINDOLE ALKALOID FROM *BLEEKERIA VITIENSIS*

(*Phytochemistry*, 1974, *13*, 503)

Phytochemistry, 1974, Vol. 13, pp. 503 to 504. Pergamon Press. Printed in England.

CARAPANAUBINE: AN OXINDOLE ALKALOID FROM *BLEEKERIA VITIENSIS**

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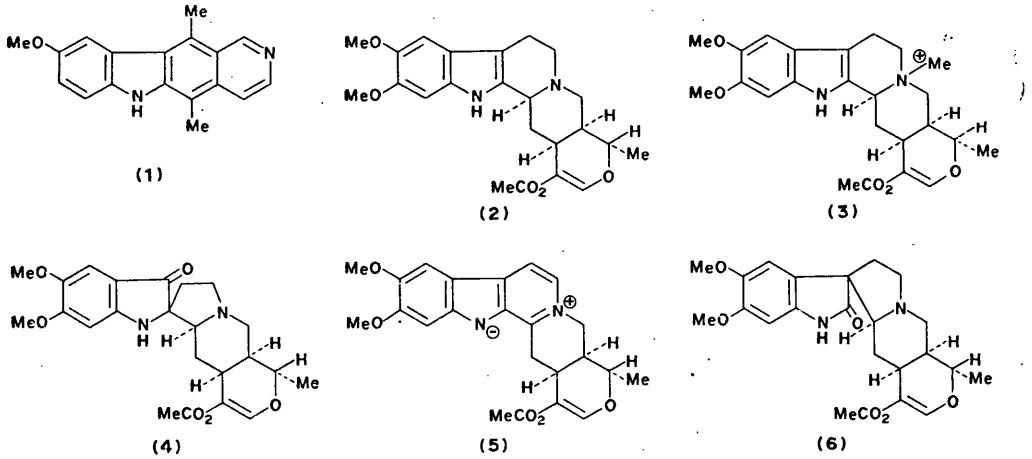
Key Word Index—*Bleekeria vitiensis*; Apocynaceae; alkaloids; carapanaubine; isoreserpiline; isoreserpiline-ψ-indoxyl; bleekerine.

Abstract—The stem-bark of *Bleekeria vitiensis* A. C. Smith contains traces of the oxindole alkaloid carapanaubine as well as isoreserpiline-ψ-indoxyl. The co-occurrence of these two compounds is of probable biosynthetic significance, representing alternative oxidative rearrangement products of the alkaloid isoreserpiline.

IN PREVIOUS work[1,2] we have shown that the Fijian plant *Bleekeria vitiensis* (Markgraf) A. C. Smith, Apocynaceae, is an abundant source of 9-methoxyellipticine (**1**) and isoreserpiline (**2**). A number of minor alkaloids are also present including holeinine (**3**), isoreserpiline-ψ-indoxyl (**4**) and bleekerine (**5**).



In this communication we report the isolation of the oxindole alkaloid carapanaubine (**6**) from the stem-bark of *B. vitiensis*. Although this alkaloid has been isolated previously from Apocynaceous plants,[3] the discovery of it together with isoreserpiline-ψ-indoxyl is unique and interesting.

The primary site of synthesis of isoreserpiline in *B. vitiensis* appears to be the leaves. In other parts of the plant the concentration is much lower.[2] Although this alkaloid is invariably

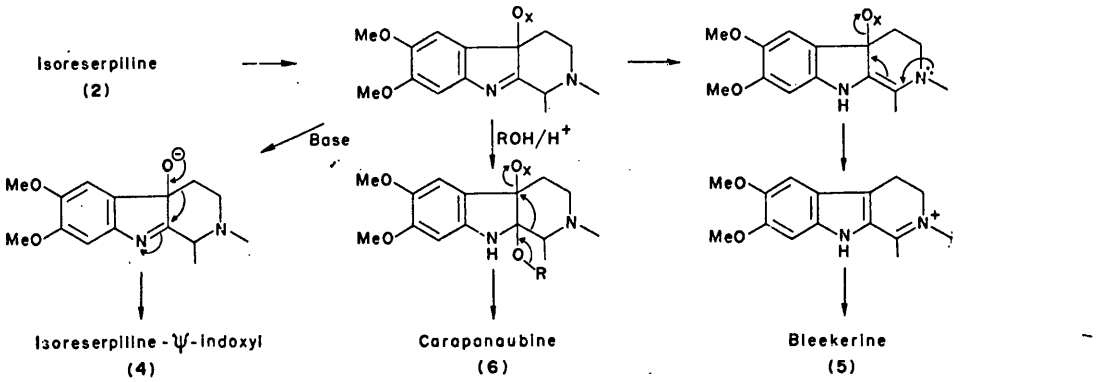
* Part III in the series "Extractives of the Ochrosiinae". For Part II see Ref. 2.

[1] KILMINSTER, K. N., SAINSBURY, M. and WEBB, B. (1972) *Phytochemistry* **11**, 389.
[2] SAINSBURY, M. and WEBB, B. (1972) *Phytochemistry* **11**, 2337.
[3] GILBERT, B., BRISSOLESE, J. A., FINCH, N., TAYLOR, W. I., BUDZIKIEWICZ, H., WILSON, J. M. and DJERASSI, C. (1963) *J. Am. Chem. Soc.* **85**, 1523.

accompanied by traces of isoreserpiline-ψ-indoxyl, holeinine, bleekerine and carapanaubine have only been detected in the stem-bark.

The regular co-occurrence of isoreserpiline and isoreserpiline-ψ-indoxyl lend support to the view that the latter is an artifact; nevertheless the distinctive chromatographic behaviour of this compound has enabled its detection in the very earliest phase of the extraction procedure. a fact which tends to substantiate its authenticity. It seems probable that carapanaubine and isoreserpiline-ψ-indoxyl form from isoreserpiline by alternative oxidative rearrangements. Such rearrangements have been observed *in vitro*; thus when the acetoxyindoleine (7, X = OAc) formed by lead tetra-acetate oxidation of isoreserpiline, is treated with methanolic acetic acid carapanaubine is produced,[4] but if base is employed isoreserpiline-ψ-indoxyl results.

Since we have shown[2] that lead tetra-acetate oxidation of isoreserpiline yields the zwitterionic alkaloid bleekerine, there appears to be a direct correlation between *in vitro* and *in vivo* reactions leading from isoreserpiline to bleekerine, carapanaubine and isoreserpiline-ψ-indoxyl. It seems likely that the biosynthetic routes leading to the ellipticine and isoreserpiline alkaloids are also intimately linked, but unfortunately, at the present time, there is no experimental evidence to verify this conclusion.



SCHEME 1. OXIDATIVE PRODUCTS OF ISORESERPILINE.

EXPERIMENTAL

Ground stem-bark (2 kg) was extracted exhaustively with MeOH (6 l.) and the conc. extract chromatographed on alumina (Merck neutral grade 1), eluting firstly with light petrol. (60–80°), then with light petrol.–$CHCl_3$ mixtures. Carapanaubine (2·5 mg) was isolated from fractions eluted with 80–100% $CHCl_3$–light petrol. where it occurred as a minor component; the principal extractives being sterols and 9-methoxyellipticine. Carapanaubine, m.p. 218–220°, m.m.p. 219–220° (lit.,[3] 221–223°) λ_{max}^{EtOH}, 244 (log ϵ 4·20) nm was obtained as colourless prisms. MS: *m/e* 428·1948 (Found: C, 64·5; H, 6·6; N, 6·5. Calc. for $C_{23}H_{28}N_2O_6$: C, 64·5; H, 6·6; N, 6·5%). This material has identical TLC properties, in three solvent systems, to an authentic sample, generously provided by Dr. B. Gilbert, Centro de Pesquisas de Productos Naturais, Brazil. In addition, the circular dichroism curve[6] of the alkaloid is superimposable upon that recorded by Pousset *et al.*[7] for carapanaubine, thus distinguishing it from the alternative diastereoisomeric forms.

Acknowledgements—The authors thank Dr. K. Jewers, Tropical Products Institute, London for the gift of plant material and the Cancer Research Campaign for financial support.

[4] FINCH, N., GEMENDEN, C. W., HSU, I. H. C. and TAYLOR, W. I. (1963) *J. Am. Chem. Soc.* **85**, 1520.
[5] FINCH, N. TAYLOR, W. I. and ULSHAFER, P. R. (1963) *Experientia* **19**, 296.
[6] We are grateful to Dr. P. M. Scopes, Westfield College, London for determining this spectrum.
[7] POUSSET, J.-L., POISSON, J., SHINE, R. J. and SHAMMA, M. (1967) *Bull. Soc. Chim. Fr.* **8**, 2766.

SYNTHESIS OF 9-AMINOELLIPTICINE

(9-AMINO-5,11-DIMETHYL-6H-PYRIDO[4,3-b]CARBAZOLE

AND RELATED COMPOUNDS

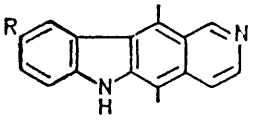
(J.Chem.Soc.Perkin 1, 1974, 1580)

Synthesis of 9-Aminoellipticine (9-Amino-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and Related Compounds

By Malcolm Sainsbury * and Brian Webb, School of Chemistry & Chemical Engineering, University of Bath, Claverton Down, Bath, Somerset

Attempts to prepare 9-nitroellipticine from 2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethylidene}-5-nitroindolin-3-one have been unsuccessful. On the other hand 9-aminoellipticine has been prepared by ring closure of 5-acetamido-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethyl}indole. The mechanism of the reduction of alkylideneindolinones by sodium borohydride is discussed and an anomalous nitration reaction of indoles in concentrated sulphuric acid is reported.

THERE is continuing interest in the antineoplastic activity of the 6*H*-pyrido[4,3-*b*]carbazole system,[1,2] and human clinical trials with the alkaloid ellipticine (1; R = H) are being conducted.[3]



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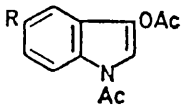

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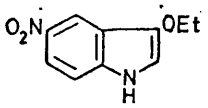

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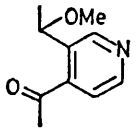

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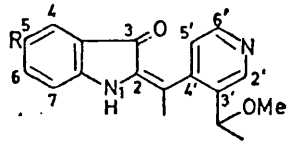

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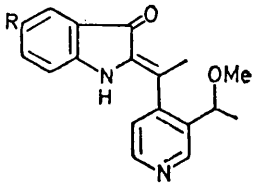
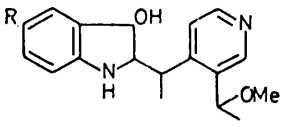


(6)

Hansch has commented recently [4] upon the difficulties surrounding the selection of those derivatives of a pharmacologically interesting molecule most likely to reveal trends in structure–activity relationships, but, taking as his examples 9-substituted ellipticines, this author indicated how by the use of substituent constants and regression analyses it is possible to make a judicious choice of targets for synthesis and bioassay.

Thus, in view of the ease by which a nitro-group can be transformed into other functions, we decided to prepare 9-nitroellipticine (1; R = NO_2) as the starting material for a series of experiments designed to evaluate some of the Hansch proposals. The first step of the synthesis required the combination of 1,3-diacetyl-5-nitroindoxyl (2; R = NO_2) with the 4-acetylpyridine (3). However, no such reaction was observed under a variety of basic and acidic conditions, although in our preliminary studies [5] the corresponding reaction between compounds (2, R = H) and (3) gave a good yield of the *E*- and *Z*-isomers (5) and (6) (R = H).

A small yield of the required isomers † was obtained when the nitroindoxyl (2; R = NO_2) was converted into the ether (4) and this was treated with the ketone (3) in aqueous hydrogen bromide. Owing to the inefficiency of this approach, however, direct nitration of a mixture of the unsubstituted isomers (5) and (6) (R = H) was attempted next. This reaction proceeded smoothly to give the corresponding nitro-derivatives in moderate yield. From our previous experience [5] we anticipated that the mixture of isomers, on reduction with sodium borohydride in boiling ethanol, would form the indoline alcohol (7; R = NO_2) and that this would be readily dehydrated to the 5-nitroindole (8; R = NO_2). In fact only the 5-aminoindole (8; R = NH_2) was isolated from the reaction product, in trace amounts together with much resinous material. Under less severe conditions the major product was



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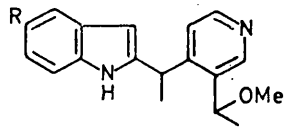
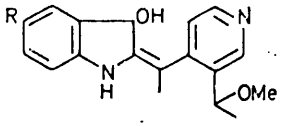
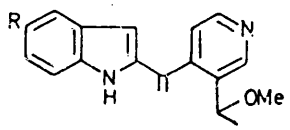


(8)



(9)



(10)

the unstable alcohol (9; R = NO_2) which upon attempted recrystallization, or on heating in benzene solution, gradually formed the vinyl derivative (10;

† Each of the isomers exists as a pair of diastereoisomers owing to the presence of the chiral centre joined to C-3 of the pyridine ring and to restricted rotation about the bond joining the enone and pyridine units of structure;[6] because of the temperature dependence of their n.m.r. spectra, it is possible to calculate potential energy barriers to rotation (see Experimental).

[1] G. Mathé, M. Hayat, F. de Vassal, L. Schwarzenberg, M. Schneider, J. R. Schlumberger, C. Jasmin, and C. Rosenveld, *Rev. Europ. Études Clin. et Biol.*, 1970, **15**, 541.

[2] J. B. Le Pecq, C. Gosse, N. Dat-Xuong, and C. Paoletti, *Compt. rend.*, 1973, **277D**, 2289.

[3] Ellipticine: N.S.C.-71,795; personal communication from R. B. Engle, National Cancer Institute, N.I.H., Bethesda, Maryland, U.S.A.

[4] C. Hansch, *Cancer Chemother. Rep.*, 1972, **56** (1), 433.

[5] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.

[6] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2415.

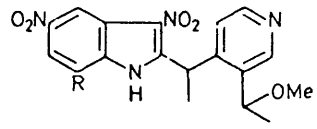
R = NO_2). We were unable to define conditions necessary to give either (7; R = NO_2) or (8; R = NO_2).

Hooper and Pitkethly [7] have shown that normally the reduction of the αβ-unsaturated system of alkylideneindolinones with sodium borohydride involves 1,4-addition of hydrogen as the first step. Therefore the formation of the alcohol (9; R = NO_2) is interesting since, unless tautomeric phenomena are involved, it suggests that this reaction involves an initial 1,2-addition of hydrogen. Certainly the selection of conditions for the reduction of alkylideneindolinones is critical and we have indications that the reduction of the isomeric mixtures (5) and (6) (R = H or NHAc) with sodium borohydride at room temperature also gives compounds (9; R = H or NHAc), whereas at higher temperatures the indoline alcohols (7; R = H or NHAc) are formed normally.

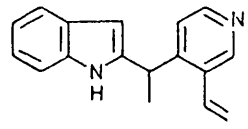
Although compound (10; R = NO_2) is at the correct oxidation level to form 9-nitroellipticine on cyclisation, attempts to bring about such a reaction with the small amount of material available failed.

Nitration of 2-substituted indoles in concentrated sulphuric acid solution affords the corresponding 5-nitroindoles,[8] and it is generally assumed [9] that initial protonation at C-3 prevents the introduction of the nitro-group at this site. When, however, the indole (8; R = H) was treated with sulphuric acid and potassium nitrate at 0°, a dinitroindole and a trinitroindole were isolated. In the n.m.r. spectra of both these products the signal anticipated for the C-3 proton [δ *ca.* 6·5 in $(CD_3)_2SO$] is absent. Each must therefore contain a nitro-substituent at this position, despite the fact that the spectrum of the parent indole (8; R = H) in 90% sulphuric acid solution shows that it is extensively protonated at C-3. Thus either there is sufficient unprotonated compound present to allow direct 3-nitration or, more probably, initial attack by the nitronium ion occurs in the benzenoid ring, resulting in a decrease in the overall basicity of the indolic system with a subsequent shift in the equilibrium between protonated and unprotonated species in favour of the latter. It is this mononitro-intermediate which then undergoes further nitration.

The precise location of the nitro-group(s) in the benzene ring of the indole system is uncertain; chemical shift data do not allow an unequivocal decision between 3,6- or 3,5- and 3,4,6- or 3,5,7-substitution patterns for the dinitro- and trinitro-derivatives, respectively. However, the u.v. spectrum of 2-methyl-3,6-dinitroindole shows maxima at 225 (ε 10,230), 291 (13,800), 306 (14,130) and 341 (14,790) nm, whereas 2-methyl-3,5-dinitroindole exhibits maxima at 251 (23,440), 314 (10,960), and 347 (10,960) nm.[10] Our dinitro-compound shows $\lambda_{max.}$ 255 (ε 22,300), 320 (10,600), 345sh (9600), and 412 (6860) nm, and on this basis we formulate, tentatively, this product as (11; R = H). Unfortunately the u.v. spectra of 2-methyl-3,4,6-trinitroindole [$\lambda_{max.}$ 294 (ε 15,850) and 347 (12,020) nm] and 2-methyl-3,5,7-trinitroindole [$\lambda_{max.}$ 284 (17,780) and 350 (9550) nm] [10] are similar, but the positions of the maxima for our trinitro-derivative [272 (17,500), 345sh (9600), and 411 (10,200) nm] are more in accord with those of 2-methyl-3,5,7-trinitroindole and thus we allocate structure (11; R = NO_2) to this product.



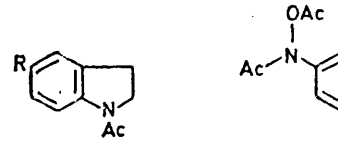
(11)



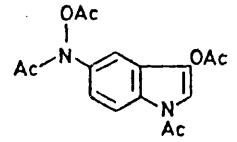
(12)

The parent indole (8; R = H) was regenerated unchanged from concentrated sulphuric acid solution at temperatures ranging from 0 to 90°, but after heating at 100° in sulphuric acid progressively less of the indole was liberated upon basification as the duration of the experiment was extended, and after 30 min the only product isolated was the 3-vinylpyridine derivative (12). No ellipticine derivatives were obtained.

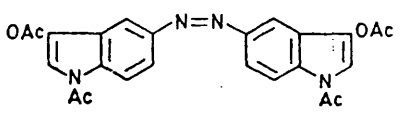
At this point we abandoned the projected synthesis of 9-nitroellipticine in favour of that of the 9-amino-analogue (1; R = NH_2). Initially we attempted to hydrogenate the nitroindoxyl (2; R = NO_2) at atmospheric pressure in acetic acid–acetic anhydride over Adams catalyst, but the product was the indoline (13; R = NHAc) or, if the acetic anhydride was omitted, (13; R = NH_2). Under milder conditions, for example in dimethylformamide solution containing acetic anhydride and with 5% palladium–carbon as catalyst, the phenylhydroxylamine derivative (14) was formed. Finally, however, repetition of the latter experiment, but in the absence of acetic anhydride and with a longer reaction time, gave the indoxyl (2; R = NH_2) in the crude state, acetylation of which with acetic anhydride gave the amide (2; R = NHAc) together with small amounts of compounds (15) and (16).



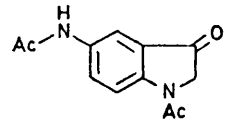
(13)



(14)



(15)



(16)

Condensation of the amide (2; R = NHAc) with the ketone (3) afforded a mixture of isomers (5) and (6)

[7] M. Hooper and W. N. Pitkethly, *J.C.S. Perkin I*, 1972, 1607.
[8] W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, 1963, **28**, 2262.
[9] W. A. Remers in 'The Chemistry of Heterocyclic Compounds,' vol. 25 (1), ed. W. J. Houlihan, Wiley-Interscience, London, 1972, p. 78.
[10] W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, 1965, **30**, 3463; 1966, **31**, 65.

(R = NHAc) in 35% yield and this, on reduction with sodium borohydride in boiling ethanol, gave the indoline alcohol (7; R = NHAc). Treatment of the alcohol with methanolic hydrogen chloride gave the indole (8; R = NHAc), which with hot aqueous 60% hydrogen bromide underwent cyclisation, dehydrogenation, and hydrolysis to yield 9-aminoellipticine, as the bis-hydrobromide, in one step. The free base was obtained on basification of the salt and from the filtrate, after removal of 9-aminoellipticine, a small quantity of ellipticine (1; R = H) was isolated. 9-Aminoellipticine and some of the derivatives described in this paper are undergoing biological examination.

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol unless otherwise stated; i.r. spectral data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at either 60 or 100 MHz with tetramethylsilane as internal standard.

1-Acetyl-5-nitroindol-3-yl Acetate (2; R = NO_2).—This compound was prepared from 2-chloro-5-nitrobenzoic acid by the published method.[11]

5-Acetamido-1-acetylindol-3-yl Acetate (2; R = NHAc).—(*a*) 1-Acetyl-5-nitroindol-3-yl acetate (200 mg) in acetic acid (70 ml) and acetic anhydride (10 ml) was hydrogenated at room temperature and atmospheric pressure, over Adams catalyst, for 2 h. Filtration and evaporation gave *1-acetyl-5-acetamidoindoline* (13; R = NHAc) as a pale yellow solid (81 mg, 48·7%), m.p. 213—215° (from ethanol), *m/e* 218, 176, and 133 (base), $\nu_{max.}$ 1690 (NAc), 1640 (NHAc), 1600, 1537, and 3300 cm^{-1} (NH), $\lambda_{max.}$ 275 (ε 25,500), 278 (25,300), 297sh (12,300), and 310sh (7840) nm, δ ($CDCl_3$) 2·1 (3H, s, NHAc), 2·2 (3H, s, NAc), 3·1 (2H, t, $J_{3,2}$ 8 Hz, 3-H_2), 4·0 (2H, t, $J_{2,3}$ 8 Hz 2-H_2), 7·0 (1H, d, $J_{5,6}$ 8 Hz, 5-H); 7·4 (1H, s, NH), 7·7 (1H, d, $J_{4,6}$ 2 Hz, 4-H), and 8·1 (1H, 2× d, $J_{6,5}$ 8, $J_{6,4}$ 2 Hz, 6-H) (Found: C, 66·1; H, 6·4; N, 12·8. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%).

(*b*) Repetition of experiment (*a*) but without acetic anhydride gave colourless prisms of *1-acetyl-5-aminoindoline* (13; R = NH_2) (35%), m.p. 165—167° (from benzene), *m/e* 176, 134, and 133 (base), $\nu_{max.}$ 1625 (CO) and 1590 cm^{-1}, $\lambda_{max.}$ 272 (ε 15,800) and 310sh (3870) nm, δ ($CDCl_3$) 2·1 (3H, s, NAc), 3·05 (2H, t, $J_{3,2}$ 8 Hz, 3-H_2), 3·3br (2H, s, NH_2), 3·95 (2H, t, $J_{2,3}$ 8 Hz, 2-H_2), 6·45 (1H, 2× d, $J_{6,7}$ 8, $J_{6,4}$ 2 Hz, 6-H), 6·50 (1H, d, $J_{4,6}$ 2 Hz, 4-H), and 8·0 (1H, d, $J_{7,6}$ 8 Hz, 7-H) (Found: C, 68·0; H, 6·9; N, 15·9. $C_{10}H_{12}N_2O$ requires C, 68·2; H, 6·9; N, 15·9%).

(*c*) Hydrogenation of (2; R = NO_2) (130 mg) in dimethylformamide (30 ml) and acetic anhydride (15 ml) over 5% palladium–carbon during 3 h gave, after work-up, a dark coloured solid. This was extracted with hot ethanol; the extract was filtered and evaporated to give *5-N-acetoxyacetamido-1-acetylindol-3-yl acetate* (14) (40 mg, 24·4%), m.p. 141—142° (from ethanol), *m/e* 332, 290, 274, 232, 230, 190, and 148 (base), $\nu_{max.}$ 1785 (NOAc), 1760, 1686 (CO), and 1195 cm^{-1} (CO) [PhNAc(OAc) shows $\nu_{max.}$ 1795, 1684, and 1186 cm^{-1}], $\lambda_{max.}$ 246 (ε 25,000), 301 (4330), and 308sh (4220) nm, δ ($CDCl_3$) 2·05 (3H, s, NAc), 2·2 (3H, s, NAc), 2·35 (3H, s, OAc), 2·60 (3H, s, OAc) 7·5 (1H, 2 × d, *J* 9 and 2 Hz, 6-H) 7·7 (1H, d, *J* 2 Hz, 4-H), 7·8 (1H, s, 2-H), and 8·55 (1H, d, *J* 9 Hz, 7-H) (Found: C, 57·8; H, 5·1; N, 8·3. $C_{16}H_{16}N_2O_6$ requires C, 57·8; H, 4·85; N, 8·4%).

(*d*) Reduction of (2; R = NO_2) as in (*c*), but in dimethylformamide alone and for 12 h, gave, on work-up, a gum. This was treated with acetic anhydride; removal of the reagent left a solid which partly dissolved in hot ethanol. The red residue was characterized as *1,1′-diacetyl-5,5′-azoindole-3,3′-diyl diacetate* (15) (100 mg, 5·7%), microcrystals, m.p. 268—270° (from chloroform), *m/e* 460, 418, 376, 174, and 132 (base), $\nu_{max.}$ 1760 (OAc), 1700 (NAc), and 1200 cm^{-1} (CO), $\lambda_{max.}$ 245sh (ε 22,800),255 (23,700), 288 (2560), and 298sh (18,700) nm, δ (CF_3·CO_2H) 2·60 (6H, s, 2 × NAc), 2·90 (6H, s, 2 × OAc), 8·20 (2H, s, 2- and 2′-H), 8·4 (2H, 2 × d, *J* 10 and 2 Hz, 6- and 6′-H), 8·60 (2H, d, *J* 2 Hz, 4- and 4′-H), and 8·9 (2H, d, *J* 10 Hz, 7- and 7′-H) (Found: C, 62·5; H, 4·4;N, 12·1. $C_{24}H_{20}N_4O_6$ requires C, 62·6; H, 4·4; N, 12·2%).

On concentration of the ethanolic extract the *acetamido-derivative* (2, R = NHAc) crystallised, giving needles (1·4 g, 67%), m.p. 221—223, *m/e* 274, 232, and 190 (base), $\nu_{max.}$ 3300 (NH), 1750 (OAc), 1710 (NAc), 1660 (NHAc), and 1210 cm^{-1} (CO), $\lambda_{max.}$ 247 (ε 20,900), 300 (4120), and 305 (4000) nm, δ ($CDCl_3$) 2·1 (3H, s, NHAc), 2·35 (3H, s, NAc), 2·55 (3H, s, OAc), 7·4 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 7·75 (1H, s, 2-H), 8·1 (1H, d, *J* 2 Hz, 4-H), and 8·45 (1H, d, $J_{7,6}$ 8 Hz, 7-H) (Found: C, 61·3; H, 5·3; N, 10·0. $C_{14}H_{14}N_2O_4$ requires C, 61·3; H, 5·1; N, 10·2%).

Further concentration of the mother liquor from which the amide (2; R = NHAc) separated gave *5-acetamido-1-acetylindoxyl* (16) (255 mg, 14·4%), m.p. 246—247° (from ethanol), $\nu_{max.}$ 1725 (NAc), 1690 (CO), and 1645 cm^{-1} (NHAc), $\lambda_{max.}$ 249 (ε 27,500), 269sh (17,700), 278 (21,500), 286sh (16,800), and 368 (3840) nm, δ [$(CD_3)_2SO$] 2·05 (3H, s, NHAc), 2·2 (3H, s, NAc), 2·5 (2H, s, 2-H_2), 7·7 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 8·0 (1H, d, *J* 2 Hz, 4-H), 8·3 (1H, d, $J_{7,6}$ 8 Hz, 7-H), and 10·1br (1H, s, NH) (Found: C, 61·95; H, 5·2; N, 12·1. $C_{12}H_{12}N_2O_3$ requires C, 62·1; H, 5·2; N, 12·1%).

3-Ethoxy-5-nitroindole (4).—The nitroindole (2; R = NO_2) (4·2 g) in ethanol (50 ml) was heated under reflux with aqueous 20% sulphuric acid (10 ml) under nitrogen for 1 h. On dilution and extraction with ether, compound (4) was obtained as a gum which slowly crystallized and was recrystallized from aqueous ethanol to give pale yellow *prisms* (30 g), m.p. 112°, *m/e* 206, 178 (base), 132, and 131, $\nu_{max.}$ 3400 (NH), 1620 (C=C), 1510 (N=O), and 1330 cm^{-1} (NO), $\lambda_{max.}$ 268sh (ε 7250), 288 (13,000), and 337 (5230) nm, δ ($CDCl_3$) 0·95 (3H, t, *J* 7 Hz, CH_2·CH_3), 3·65 (2H, q, *J* 7 Hz, CH_2·CH_3), 6·6 (1H, s, 2-H), 7·0 (1H, d, *J* 9 Hz, 7-H), 7·55 (1H, 2 × d, *J* 9 and 2·5 Hz, 6-H), and 8·05 (1H, d, *J* 2·5 Hz, 4-H) (Found: C, 58·0; H, 5·0; N, 13·5. $C_{10}H_{10}N_2O_3$ requires C, 58·25; H, 4·9; N, 13·6%).

(E)- *and* (Z)-2-{1-[3-(*1-methoxyethyl*)-*4-pyridyl*]*ethylidene*}-*5-nitroindolin-3-one* [(5) *and* (6) (R = NO_2)].—(*a*) A mixture of 3-ethoxy-5-nitroindole (4·8 g) and 4-acetyl-3-(1-methoxyethyl)pyridine (4·3 g) [5] in aqueous 10% hydrogen bromide (125 ml) was refluxed for 10 min under nitrogen atmosphere and then kept at room temperature for 72 h. Basification and extraction with chloroform furnished a red oil, together with a considerable amount of a deep purple insoluble solid which could not be purified. Trituration of the oil with ethanol afforded the *E*-isomer (5; R = NO_2), m.p. 250° (decomp.) (from ethanol), and evaporation of the ethanolic filtrate gave the *Z*-isomer (6; R = NO_2), m.p. 225—230°; total yield 4%; *m/e* 339, 307 (base), 292, and 280.

The (E)-*isomer* showed $\nu_{max.}$ 1688 (CO), 1630 (C=C),

[11] S. J. Holt and V. Petrow, *J. Chem. Soc.*, 1947, 607.

1505, and 1325 cm^{-1}, $\lambda_{max.}$ 256 (ε 12,500), 266 (12,900), 287sh (14,000), 297 (15,100), 372 (10,100), 420sh (5900), and 444 (5150) nm, δ ([$^2H_5$]pyridine; 30°) 1·45 and 1·51 (3H, 2 × d, *J* 6 Hz, CH·C*H*$_3$), 2·32 and 2·38 (3H, 2 × s, C·C*H*$_3$), 3·19 and 3·28 (3H, 2 × s, OMe), *ca.* 4·6 (1H, 2 × interleaving q, C*H*·CH$_3$), 7·02 (1H, d, *J* 8·5 Hz, 7-H), 7·20 (1H, d, *J* 5 Hz, 5′-H), 8·32 (1H, 2 × d, *J* 8·5 and 2·0 Hz, 6-H), 8·56 (1H, d, *J* 2·0 Hz, 4-H), 8·6 (1H, d, *J* 5 Hz, 6′-H), and 9·12 (1H, s, 2′-H). From the temperature dependence of this spectrum, E_a, the potential energy barrier to rotation, is calculated to be 71 kJ mol^{-1}.

The (Z)-*isomer* showed $\nu_{max.}$ 1695 (CO), 1635 (C=C), 1605, 1515, and 1325 cm^{-1} (the electronic spectra of *E* and *Z*-isomers are identical), [(CD$_3$)$_2$SO; 30°] 1·35 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 3·1 (3H, s, C·CH$_3$), 3·3 (3H, s, OMe), *ca.* 4·3 (1H, q, C*H*·CH$_3$), 7·0 (1H, d, *J* 9 Hz, 7-H), 7·3 (1H, d, *J* 5 Hz, 5′-H), 8·2 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·25 (1H, d, *J* 2 Hz, 4-H), 8·6 (1H, d, *J* 5 Hz, 6′-H), 8·7 (1H, s, 2′-H), and 9·7 (1H, s, NH). In the case of this isomer the n.m.r. spectrum obtained was that of the enantiomeric mixture, the coalescence temperature being below 30° (Found: C, 63·5; H, 5·0; N, 12·5. $C_{18}H_{17}N_3O_4$ requires C, 63·7; H, 5·05; N, 12·4%).

(*b*) The indolinone (6; R = H) (2 g) in concentrated sulphuric acid (6 ml) at 0° was treated dropwise with potassium nitrate (1·2 mol. equiv.) in concentrated sulphuric acid during 10 min. The mixture was then poured on ice (30 g), basified with sodium hydrogen carbonate, and extracted with chloroform to give, after removal of solvent, a red gum which was worked up to give a mixture of (5) and (6) (R = NO_2) (750 mg).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethylidene*}-5-*nitroindolin*-3-*ol* (9; R = NO_2).—The indolinones (5) and (6) (R = NO_2) (500 mg) in 95% ethanol (50 ml) were treated with sodium borohydride in portions at room temperature. After 15 min the solvent was evaporated off and the residue partitioned between chloroform and water. Concentration of the chloroform layer afforded a red gum which when triturated with ether gave an orange solid. This when recrystallized from ethanol provided deep red crystals (76 mg), m.p. 194—195° (subsequent crops from the mother-liquor were yellow and melted in the range 145—155°), *m/e* 341 (v. weak), 323, 307, 292 (base), and 278, $\nu_{max.}$ *ca.* 3320, 1620, 1510, 1320, and 1180 cm^{-1}, $\lambda_{max.}$ 254 (ε 8950) and 410 (15,400) nm, δ [(CD$_3$)$_2$SO] 1·40 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 2·0 (3H, s, CH$_3$), 3·2 (3H, s, OMe), 4·5 (1H, q, *J* 6 Hz, C*H*·CH$_3$), 5·6 [1H, s, C(OH)*H*], 6·8 (1H, d, *J* 7 Hz, 5′-H), 7·25 (1H, d, *J* 8 Hz, 7-H), 8·0 (1H, d, *J* 2 Hz, 4-H), 8·15 (1H, 2 × d, *J* 7 and 2 Hz, 6-H), 8·45 (1H, d, *J* 7 Hz, 6′-H), 8·6 (1H, s, 2′-H), and 9·75 (1H, s, NH) (an additional peak, probably due to OH plus water, is observed at δ 3·1). This material could not be dried (see later) and consistent analytical figures were not obtained.

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*vinyl*-5-*nitroindole* (10; R = NO_2).—A solution of the alcohol (9; R = NO_2) (50 mg) in dry benzene was heated in a Dean–Stark apparatus for 12 h. Removal of the solvent and crystallization of the residue from aqueous ethanol gave (10; R = NO_2) as yellow *prisms* (22 mg, 46·5%), m.p. 239°, *m/e* 323, 291 (base), and 276, $\nu_{max.}$ 1620sh, 1610, 1592, 1515, 1330, and 1110 cm^{-1}, $\lambda_{max.}$ 288sh (ε 36,800), 293 (37,800), 310sh (13,070), and 341 (9950) nm, δ (CDCl$_3$) 1·3 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 3·0 (3H, s, OMe), 4·35 (1H, q, *J* 6 Hz, CH·CH$_3$), 5·3 and 6·2 (2H 2 × s, C=CH$_2$), 6·21 (1H s, 3-H), 7·25 (1H, d, *J* 5 Hz, 5′-H), 7·5 (1H, d, *J* 9 Hz, 7-H), 8·0 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·45 (1H, d, *J* 2 Hz, 4-H), 8·55 (1H, d, *J* 5 Hz, 6′-H), and 8·7 (1H, s, 2′H) (Found: C, 67·2; H, 5·3; N, 12·7. $C_{18}H_{17}N_3O_3$ requires C, 66·9; H, 5·3; N, 13·0%).

5-*Amino*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (8; R = NH_2).—Reduction of the indolinones (5) and (6) (R = NO_2) with sodium borohydride in boiling ethanol gave, on work-up, a small amount of an almost colourless solid [*m/e* 295, 248 (base), and 233], which on acetylation afforded (8; R = NHAc) (see later).

2-{1-[3-(1-*Methoxylethyl*)-4-*pyridyl*]*ethyl*}-3,5-*dinitroindole* (11; R = H).—The indole (8; R = H) (1·2 g) in concentrated sulphuric acid (10 ml) * was treated dropwise with a solution of potassium nitrate (1·2 mol. equiv.) in sulphuric acid at 0°. After the addition (*ca.* 30 min), the mixture was poured on ice, basified, and extracted with ethyl acetate. Evaporation of the extract and trituration of the residue with ether afforded a yellow solid which crystallized from acetone as *prisms* (486 mg), m.p. 140° (decomp.), *m/e* 370 (weak), 323, and 292 (base), $\nu_{max.}$ 1600, 1540, 1520, 1350, and 1105 cm^{-1}, $\lambda_{max.}$ 255 (ε 22,300), 320br (10,600), and 412 (6860) nm, δ (CDCl$_3$) 1·45 [3H, d, *J* 7 Hz, CH(OMe)·C*H*$_3$], 1·74 and 1·70 (3H, 2 × d, *J* 7 Hz, CH·C*H*$_3$) (diastereoisomerism; see ref. 6), 3·1 and 3·2 (3H, 2 × s, OMe), 4·85br [1H, q, *J* 7 Hz, C*H*(OMe)·CH$_3$], 5·5br (1H, q, *J* 7 Hz, C*H*·CH$_3$), 7·05 (1H, m, 5′-H), 7·8 (1H, d, *J* 9 Hz, 7-H), 8·25 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·45br (1H, d, *J* 5 Hz, 6′-H), 8·6 (1H, s, 2′-H), and 8·9 (1H, d, *J* 2 Hz, 4-H) (Found: C, 58·2; H, 4·9; N, 15·1. $C_{18}H_{15}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethyl*}-3,5,7-*trinitroindole* (11; R = NO_2).—The foregoing reaction was repeated with 4 mol. equiv. of potassium nitrate. After purification, the product (11; R = NO_2) was obtained as yellow *prisms* (60%), m.p. 235° (decomp.) (from ethanol) *m/e* 415, 368, 337 (base), and 321, $\nu_{max.}$ *ca.* 3400 (EtOH, NH), 1600, 1540, and 1105 cm^{-1}, $\lambda_{max.}$ 272 (ε 17,800), 330 (11,500), and 411 (10,200) nm, δ [(CD$_3$)$_2$SO] 1·0 (3H, t, *J* 7 Hz, C*H*$_3$·CH$_2$·OH), 1·4 (3H, d, *J* 6·5 Hz, C*H*$_3$·CH(OMe)], 1·17 (3H, d, *J* 6·5 Hz, C*H*$_3$C), 3·1 (3H, s, OMe), 3·5 (2H, q, *J* 7 Hz, CH$_3$·C*H*$_2$·OH), 4·8 [1H, q, *J* 6·5 Hz, C*H*(OMe)Me], 5·5 (1H, q, *J* 6 Hz, C*H*·CH$_3$), 7·0 (1H, d, *J* 5 Hz, 5′-H), 8·35 (1H, s, 4-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), and 8·7 (2H, s, 6- and 2′-H) (Found: C, 52·3; H, 4·9; N, 15·1. $C_{18}H_{17}N_5O_7$,C_2H_5OH requires C, 52·1; H, 5·0; N, 15·2%).

2-[1-(3-*Vinyl*-4-*pyridyl*)*ethyl*]*indole* (12).—The indole (8; R = H) (200 mg) in concentrated sulphuric acid (10 ml) was heated for 30 min at 100°, cooled, and poured on ice. Basification and extraction with ether yielded (12) as *prisms* (152 mg, 86%), m.p. 140—141°, *m/e* 248 and 233 (base), $\nu_{max.}$ 3110, 1625, 1610, and 1540 cm^{-1}, $\lambda_{max.}$ 260 (ε 11,900), 280sh (10,500), and 293 (8100) nm, δ (CDCl$_3$) 1·6 (3H, d, *J* 7 Hz, CH·C*H*$_3$), 4·4 (1H, q, *J* 7 Hz, C*H*·CH$_3$), 5·25, 5·4, and 5·7 (2H, 3 × d, *J* 1·5 Hz, CH=C*H*$_2$), 6·4br (1H, s, 3-H), 6·7—7·2 (5H, m, 4-, 5-, 6-, and 5′-H, and C*H*=CH$_2$), 7·5 (1H, m, 7-H), 8·25 (1H, d, *J* 5 Hz, 6′-H), 8·5 (1H, s, 2′-H), and 8·7br (1H, s, NH) (Found: C, 82·4; H, 6·7; N, 11·3. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·7; N, 11·3%).

(E)-5-*Acetamido*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethylidene*}*indolin*-3-*one* (5; R = NHAc).—To a mixture of the

* The n.m.r. spectrum of the indole (8; R = H) in sulphuric acid exhibits a broad two-proton singlet at δ 4·0. This is absent in the spectrum of a solution in deuteriochloroform, where the C-3 proton gives a clearly defined singlet at δ 6·4.

indoxyl (2; R = NHAc) (2 g) and the ketone (3) (1 mol. equiv.) in methanol (60 ml) under nitrogen was added potassium hydroxide (15·6 g) in water (60 ml). The mixture was then sealed up and left for 7 days, and the *product* was then filtered off under nitrogen; yield 0·7 g (27·8%), m.p. 232—234°, *m/e* 351, 304 (base), 292, and 262, $\nu_{max.}$ 1673 (CO), 1630 (NAc), and 1605 cm^{-1} (C=C), $\lambda_{max.}$ 269 (ε 22,100), 290sh (14,500), and 488 (3440) nm, δ [$(CD_3)_2SO$] 1·2 and 1·3 (3H, 2 × d, *J* 7 Hz, CH·CH_3), 2·1 and 2·15 (3H, 2 × s, C·CH_3), 3·0 and 3·1 (3H, 2 × s, OMe), 4·3 (1H, q, *J* 7 Hz, C*H*·CH_3), 7·05 (1H, d, *J* 8 Hz, 7-H), 7·1 (1H, d, *J* 5 Hz, 5′-H), 7·65 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 7·75 (1H, d, *J* 2 Hz, 4-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), 8·65 (1H, s, 2′-H), 9·4br (1H, s, NH), and 9·9br (1H, s, NHAc) (Found: C, 68·1; H, 5·95; N, 11·9. $C_{20}H_{21}N_3O_3$ requires C, 68·4; H, 6·0; N, 12·0%). In other experiments an extractive work-up, rather than filtration, was employed; in such cases a mixture of *E*- and *Z*-isomers was isolated which were not separated but used directly.

5-Acetamido-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethyl}indole (8; R = NHAc).—The indolinone mixture [(5) and (6) (R = NHAc)] was reduced with sodium borohydride in boiling ethanol and the product (7; R = NHAc), in ether was treated with hydrogen chloride. Evaporation, and crystallization of the residue from acetone and petroleum (b.p. 60—80°) afforded (8; R = NHAc) as *prisms* (66%), m.p. 222—223°, *m/e* 337, 308, and 291 (base), $\nu_{max.}$ 3220 (NH), 1660 (NAc), 1590, and 1545 cm^{-1}, $\lambda_{max.}$ 243 (ε 31,200), 301 (9000), and 311 (8300) nm, δ [$(CD_3)_2SO$] 1·3 and 1·35 [3H, 2 × d, *J* 7 Hz, CH(OMe)·CH_3], 1·6 (3H, d, *J* 7 Hz, CH·CH_3), 2·0 (3H, s, NHAc), 3·08 and 3·12 (3H, 2 × s, OMe), 4·6 (1H, q, *J* 7 Hz, C*H*·CH_3), 4·8 [1H, q, *J* 7 Hz, C*H*(OMe)·CH_3], 6·15 (1H, s, 3-H), *ca.* 7·2 (3H, m, 6-, 7-, and 5′-H), 7·7 (1H, d, *J* 2 Hz, 4-H), 8·4 (1H, d, *J* 5 Hz, 6′-H), 8·5 (1H, s, 2′-H), 9·65 (1H, s, NH), and 10·7 (1H, s, N*H*Ac) (Found: C, 71·0; H, 6·8; N, 12·4. $C_{20}H_{23}N_3O_2$ requires C, 71·2; H, 6·9; N, 12·45%).

9-Aminoellipticine (*9-Amino-5,11-dimethylpyrido*[4,3-b]*carbazole*) (1; R = NH_2).—The indole (8; R = NHAc) (140 mg) in aqueous 60% hydrobromic acid (4 ml) was heated under reflux for 18 h. The yellow product was then filtered off, dissolved in water, basified with sodium hydrogencarbonate, and extracted with ethyl acetate.* The solvent was removed and the residue was crystallized from benzene to give *9-aminoellipticine benzene solvate* (63 mg) as yellow prisms, m.p. 255—260° (decomp.), *m/e* 261 (base), $\nu_{max.}$ 3125 (NH), 1615, and 1595 cm^{-1}, $\lambda_{max.}$ 253 (ε 12,600), 283 (36,800), 297·5 (42,500), 341 (6370), 358sh (4150), and 420 (3240) nm, δ ($CDCl_3$) 2·7 (3H, s, 5-Me), 3·2 (3H, s, 11-Me), 4·8br (2H, s, NH_2), 6·9 (1H, d, *J* 8 Hz, 8-H), 7·3 (1H, d, *J* 8 Hz, 7-H), 7·65 (1H, s, 10-H), 7·8 (1H, d, *J* 6 Hz, 4-H), 8·35 (1H, d, *J* 6 Hz, 3-H), 9·6 (1H, s, 1-H), and 10·8 (1H, s, NH) [Found (sample dried at 100° for 10 h under high vacuum): C, 78·0; H, 5·7; N, 16·1. $C_{17}H_{15}N_3$ requires C, 78·1; H, 5·8; N, 16·1%].

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[3/2610 *Received*, 28*th December*, 1973]

* Re-extraction of the aqueous extract from which 9-aminoellipticine was obtained with chloroform gave ellipticine (1; R = H) (21 mg), m.p. 309—312° (lit.,[5] 309—312°).

AN IMPROVED SYNTHESIS OF 6H-PYRIDO[4,3-b]CARBAZOLES

(J.Chem.Soc.Perkin 1, 1975, 289)

An Improved Synthesis of 6*H*-Pyrido[4,3-*b*]carbazole Derivatives

By Malcolm Sainsbury,* Brian Webb, and Raymond Schinazi, School of Chemistry, University of Bath, Claverton Down, Bath

During the acid-catalysed cyclization of 5-bromo- and 5-amino-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethylidene}-indolin-3-ones to the corresponding 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines), loss of the substituent on the benzenoid ring severely reduces the product yield. The mechanism of this reaction is discussed, and the problem has been solved by modification of the side chain at position 3 of the pyridyl group. An oxidative mode of ring closure is employed and ellipticine and 9-acetamidoellipticine have thus been prepared. In general, product yields compare favourably with other routes to the 6*H*-pyrido[4,3-*b*]carbazole system. 9-Phenylellipticine has also been prepared and some circumstantial evidence for the mode of action of ellipticines in neoplastic systems is presented.

RECENTLY we described the synthesis of ellipticine (9; R = H) [1] and 9-aminoellipticine (9; R = NH_2) [2] by the route outlined in Scheme 1; these compounds show anticancer activity [3] and we intended to use the method to prepare a number of other derivatives for biological testing.

As a general synthesis of 6*H*-pyrido[4,3-*b*]carbazoles, however, our route suffers from a number of disadvantages. First, the reductive acetylation [4] and subsequent oxidation of 3-(1-methoxyethyl)pyridine (1) involves several steps, not shown in the Scheme, and the overall yield of the intermediate (2) is poor. Secondly, since the conditions required for the ring closure of the indoles (7) to 5,11-dihydroellipticines (8) (60% aqueous hydrobromic acid at 100° for several hours) are severe, only 6*H*-pyrido[4,3-*b*]carbazoles containing relatively stable substituents survive this treatment. In addition, in the formation of 9-aminoellipticine from the indole (7; R = NHAc) a substantial quantity of ellipticine accompanies the desired product.[2]

The production of ellipticine in this reaction is interesting since the direct removal of an amino-substituent from an aromatic nucleus requires a reductive mechanism. In

[1] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.

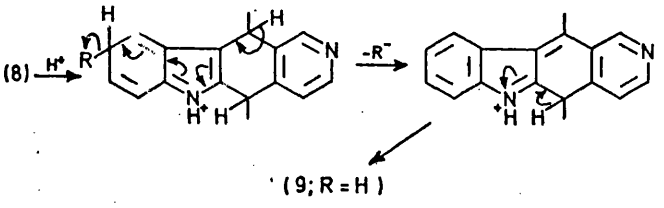
[2] M. Sainsbury and B. Webb, *J.C.S. Perkin I*, 1974, 1580.

[3] M. Hayat, G. Mathe, M. M. Janot, P. Potier, N. Dat-Xuong, A. Cavé, T. Sevenet, C. Kan-Fan, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, 1974, **21**, 101, and references cited therein.

[4] J. P. Wibaut and J. F. Arens, *Rec. Trav. chim.*, 1941, **60**, 119.

the absence of introduced reducing agents, deamination must be associated with the oxidation of the primary cyclization product (8; R = NH_2), which is not normally isolated, possibly as shown in Scheme 2.

Ellipticine is the main product when the bromoindole (7; R = Br) is treated with hydrobromic acid, but in this case evidence was also obtained (see Experimental section) for the presence of a 9-bromodemethylellipticine



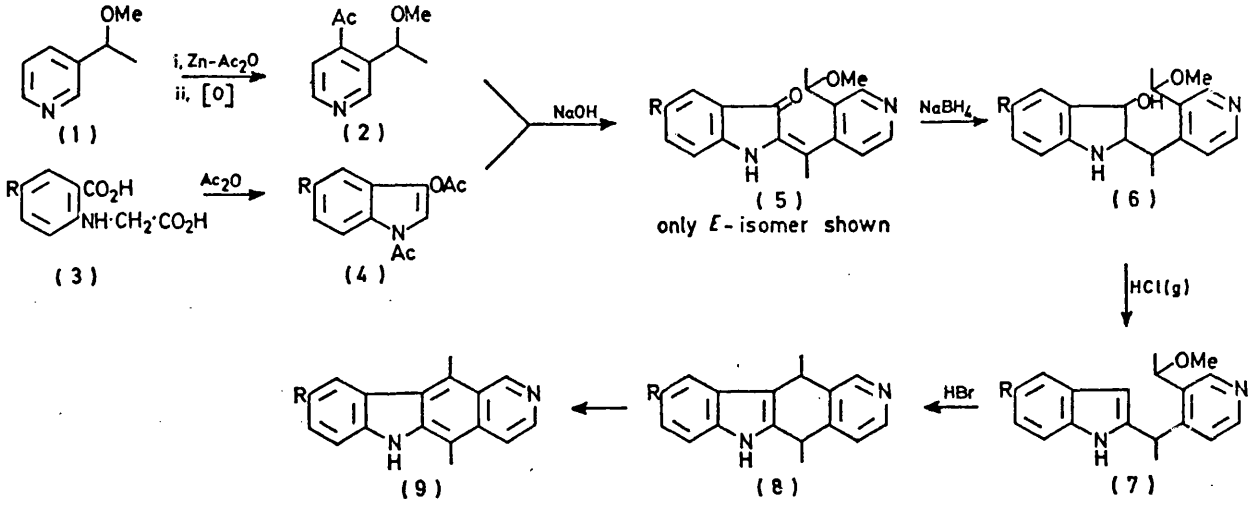
(9; R = H)

SCHEME 2

and a demethylellipticine, as well as 9-bromoellipticine (9; R = Br), in the reaction mixture. Clearly demethylation as well as deprotonation can occur during treatment with hydrobromic acid, but no ellipticine or demethyl derivatives were found when 9-phenylellipticine (9; R = Ph) was obtained from (7; R = Ph). This is to be expected, however, since displacement of the phenyl group is much less likely than of either an amino- or a halogeno-substituent.

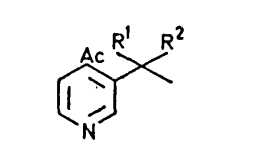
In view of these limitations to our original approach we decided to replace the ether (2) in Scheme 1 by a more accessible intermediate which when incorporated as a 2-substituent into a suitable indole derivative would require less vigorous cyclization conditions. 3,4-Diacetylpyridine (10) and the acetal (11) seemed to meet the latter requirement and an efficient route to these compounds was sought.

4-Bromo- and 4-iodo-pyridines react with butyllithium and acetonitrile to form 4-acetylpyridines;[5] 4-chloropyridines do not react under these conditions, but chloro-substituents attached to the pyridine nucleus may be exchanged by treatment with potassium iodide.[6] In view of the reported conversion of 3-methylpyridine *N*-oxide into 4-chloro-3-methylpyridine with phosphoric trichloride,[7] our first approach was to heat the *N*-oxide (12) with this reagent, in anticipation of forming (13),

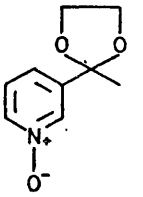


SCHEME 1

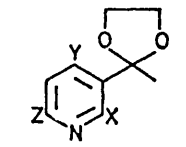
which by halogen exchange *etc.* could be converted into (10). The reaction product, however, was a mixture which probably contains the 2- and 6-chloropyridines (14) and (15), the tetracyclic compound (16), and traces of



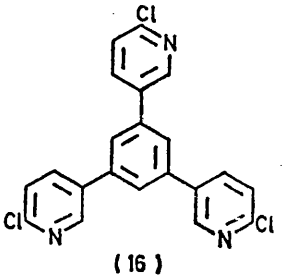
(10) R^1 R^2 = O
(11) R^1 R^2 = O·CH_2·CH_2·O



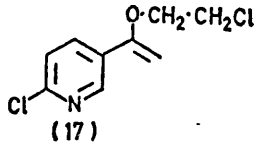
(12)



(13) X = Z = H, Y = Cl
(14) Y = Z = H, X = Cl
(15) X_1 = Y = H, Z = Cl



(16)



(17)

compound (17). No 4-chloropyridine derivatives were detected.

[5] J. P. Wibaut and L. C. Heeringe, *Rec. Trav. chim.*, 1955, **74**, 1003.

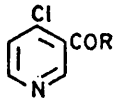
[6] E. Klingsberg, *J. Amer. Chem. Soc.*, 1950, **72**, 1031.

[7] T. N. Riley, D. B. Hale, and M. C. Wilson, *J. Pharm. Sci.*, 1973, **62**, 983.

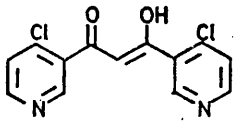
Next the known[8] acid chloride (18) was prepared as the hydrochloride salt and treated with an excess of dimethylcadmium. It was hoped to obtain 3-acetyl-4-chloropyridine (19), but the only product isolated was the stable enol (21) and, although the structure of this compound suggests that some ketone (19) is generated during the reaction, a number of modifications to the conditions failed to provide an efficient route to this compound. On one occasion, when the acid chloride salt was treated with an excess of triethylamine and the product treated directly with dimethyl cadmium, the secondary amide (20) was obtained.

Pyridine-2,5-dicarbonyl chloride affords 2,5-diacetylpyridine when treated with dimethylcadmium;[9] consequently it was anticipated that 3,4-diacetylpyridine might be obtained similarly from pyridine-3,4-dicarbonyl chloride. Such a reaction, however, gave only the lactone (22), identical with the compound obtained by the action of methylmagnesium bromide upon pyridine-3,4-dicarboxylic anhydride.[10]

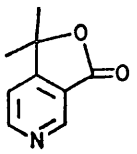
A further potential route to the required intermediate (10) or (11) was based upon the observation that *N*-alkoxypyridinium salts react with cyanide ion to afford 4-cyanopyridines[11] and such compounds combine with methylmagnesium bromide to give 4-acetyl derivatives. Thus 3-acetyl-1-ethoxypyridinium bromide (23) was prepared and treated with sodium cyanide in aqueous solution, but instead of a single product a complex mixture



(18) R = Cl
(19) R = Me
(20) R = NEt_2



(21)

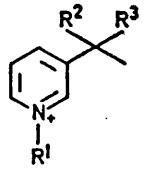


(22)

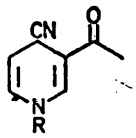
was obtained. Similar results were obtained with the acetal (24).

If 3-acetyl-1-benzylpyridinium bromide is treated with sodium cyanide the 4-cyano-1,4-dihydropyridine (26) is formed.[12] Oxidation and *N*-debenzylaton of this should give 3-acetyl-4-cyanopyridine, but attempts to effect the conversion failed with both this compound and the *para*-nitrobenzyl analogue (27). It is interesting, however, that when the latter was treated with dilute hydrochloric acid, hydrolysis to the amide (28) occurred (*cf.* Anderson and Berkelhammer[12]).

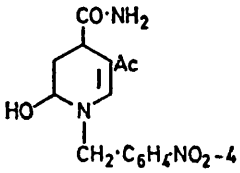
Recently Suzue *et al.*[13] have shown that 4-cyanopyridines may be prepared by the action of potassium cyanide and ammonium chloride upon 1-(*N*-methylacetamido)pyridinium salts, the latter being obtained



(23) R^1=OEt, R^2R^3=O
(24) R^1=OEt, R^2R^3=O·CH_2·CH_2·O
(25) R^1=Bz, R^2R^3=O



(26) R = $PhCH_2$
(27) R = 4-NO_2·C_6H_4·CH_2



(28)

from the corresponding pyridines by treatment with hydroxylamine-*O*-sulphonic acid followed by acetylation and methylation (Scheme 3).

When 3-acetylpyridine was treated with hydroxylamine-*O*-sulphonic acid the product was a mixture of the oximes (29) and (31), whereas the acetal (30) gave mainly 3-acetylpyridine.

Eventually, however, the intermediate (32) was obtained in good yield by the action of *O*-mesitylsulphonylhydroxylamine[14] and acetic anhydride upon (30). Completion of the sequence (steps c and d of Scheme 3) then gave the cyano-acetal (34) in 77% overall yield from (30). Attempts to convert (34) into the corresponding acetyl compound with methylmagnesium bromide gave unsatisfactory results, but by use of methyl-lithium an almost quantitative conversion into the imine (35) was effected. Treatment of this with dilute acetic acid at 100° for 20 min gave the acetal (36), whereas similar treatment with dilute hydrochloric acid yielded 3,4-diacetylpyridine.

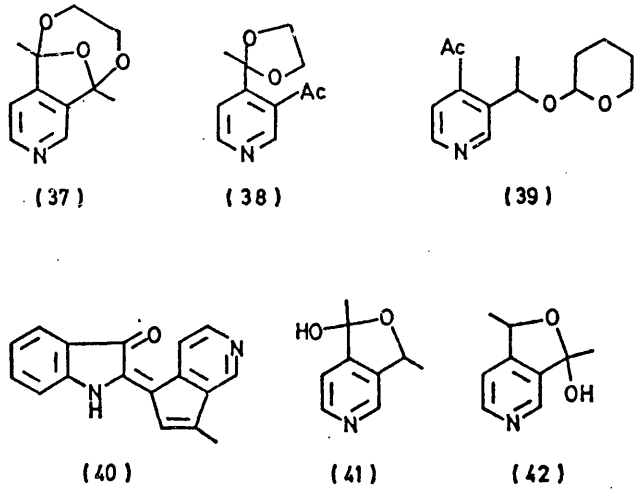
When this last compound was treated with 1 mol. equiv. of ethane-1,2-diol and toluene-*p*-sulphonic acid in benzene the tricyclic compound (37) was obtained, accompanied by (36) and the 3-acetyl isomer (38).

We speculated that an acid-catalysed condensation between indole and 3,4-diacetylpyridine might lead directly to ellipticine. However, no identifiable products were obtained from such a reaction and when 3,4-diacetylpyridine interacted with 1,3-diacetylindoxyl in aqueous sodium hydroxide solution a red gum was

[8] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, 1954, **19**, 1633.
[9] T. S. Gardner, E. Weris, and J. Lee, *J. Org. Chem.*, 1961, **26**, 1514.
[10] W. V. Ligon, Ph.D. Thesis, University of Virginia, 1970.
[11] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.
[12] A. G. Anderson, jun., and G. Berkelhammer, *J. Amer. Chem. Soc.*, 1958, **80**, 992; *J. Org. Chem.*, 1958, **23**, 1109.
[13] S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, 1973, **93**, 1331.
[14] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, **40**, 4133.

formed. This multicomponent mixture was chromatographed on alumina to give a small amount of a compound allocated structure (40).

Disappointingly, an attempted condensation between (36) and 1,3-diacetylindoxyl failed, and models showed that this failure is probably due to the steric hindrance which the rigid acetal function imparts to the 4-acetyl group. Such a constraint is much less if a single bond is attached to the α-carbon atom of the C-3 side chain and so the reactions of Scheme 3 were modified to give the tetrahydropyran derivative (39). Treatment of this

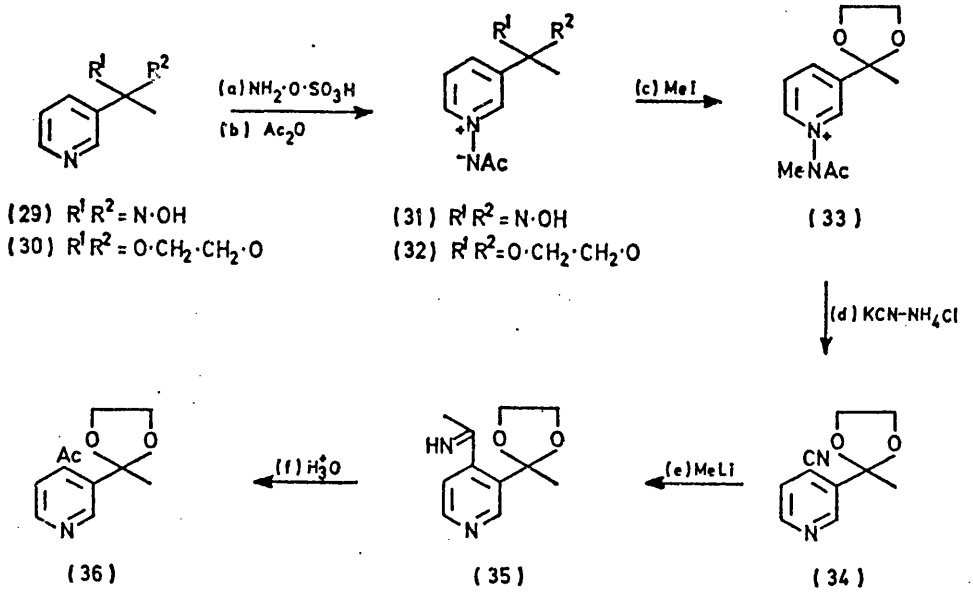


(37) (38) (39)

(40) (41) (42)

product with dilute hydrochloric acid at 100° gave the hemiacetal (41), and similarly when the acetal (36) was reduced with sodium borohydride, and the product hydrolysed with dilute hydrochloric acid, the isomeric compound (42) was obtained.

The acetylpyridine (39) reacted smoothly with 1,3-diacetylindoxyl in aqueous sodium hydroxide solution to give the indoxylidene (43); when this was reduced with sodium borohydride in ethanol at room temperature and the product treated with hydrogen chloride, the ether (46) was obtained. The formation of (46) results from incomplete reduction of the indoxylidene followed by cleavage of the protecting group to give an intermediate, *e.g.* (45), which then undergoes ring closure,



SCHEME 3

However, when the reduction was repeated, this time in ethanol at the b.p., the desired indolinol (47) was obtained, which with hydrogen chloride gave the indole (49). This product, when oxidized with manganese dioxide in dichloromethane, afforded ellipticine (9; R = H), albeit in low yield. Other oxidation attempts with lead tetra-acetate or chromium trioxide in pyridine, or under Oppenauer conditions, failed to form either ellipticine or the ketone (51), whereas treatment with potassium dichromate in acetic acid gave the indoxyl derivative (52), probably *via* initial 3-protonation, nucleophilic attack on the 2-position of the indolinium cation by the hydroxy-group, and finally oxidation at C-3.

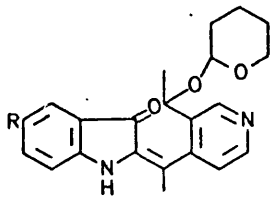
When the indole (49) was treated with phosphoric trichloride in pyridine, 5,11-dihydroellipticine (8; R = H) was formed; this is relatively stable but slowly undergoes aerial oxidation to ellipticine, particularly in the presence of silica.

Finally, when the indole (49) was treated with dimethyl sulphoxide and acetic anhydride, ellipticine was obtained in good yield.

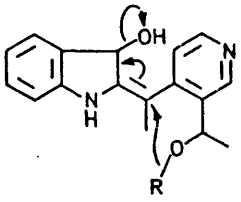
When the entire sequence was repeated using (44) and its *Z*-isomer, 9-acetamidoellipticine was prepared; the yield in the final step was 65%.

9-Aminoellipticine shows activity comparable to that

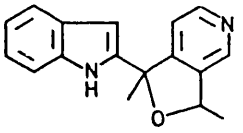
of 9-methoxyellipticine against the leukaemic mouse, whereas 9-phenylellipticine is inactive. The latter observation supports the view [15] that the anticancer activity of 6*H*-pyrido[4,3-*b*]carbazoles depends upon their intercalation between the base pairs of doubly



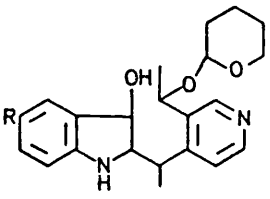
(43) R = H
(44) R = NHAc
only *E*-isomers shown



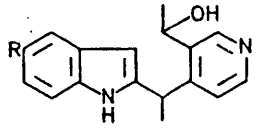
(45)



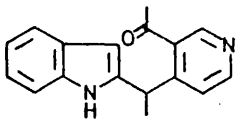
(46)



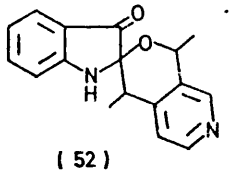
(47) R = H
(48) R = NHAc



(49) R = H
(50) R = NHAc



(51)



(52)

stranded DNA. From a consideration of models, 9-phenylellipticine may not readily form such an intercalation complex and thus should be comparatively inactive.

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol, and i.r. spectral data refer to Nujol mulls. ^{1}H N.m.r. spectra were recorded at either 60 or 100 MHz with tetramethylsilane as internal standard.

4-Acetamidobiphenyl-3-carbonitrile.— 4-Acetamido-3-bromobiphenyl [16] (72·5 g) and copper(I) cyanide (26·7 g) in dimethylformamide were heated under reflux for 6 h. After partial cooling the mixture was poured slowly into a warm solution of sodium cyanide (50 g) in water (250 cm^3); this was stirred vigorously for 2 h and then extracted with chloroform (500 cm^3). The organic phase was washed with aqueous 10% sodium cyanide (100 cm^3), then with water, dried, and evaporated to give the *nitrile* as needles, m.p. 161—162° (46 g, 79%), *m/e* 236 (base, M^+), 213, 195, 167, and 139; $\nu_{max.}$ 3320 (NH), 2240 (CN), and 1680 cm^{-1} (CONH); δ [(CD$_3$)$_2$SO] 8·62 (1H, d, *J* 9 Hz, 5-H), 7·95 (2H, m, 2- and 6-H), 7·65 (5H, m, 1-Ph), and 2·45 (3H, s, Ac) (Found: C, 76·25; H, 5·1; N, 6·8. $C_{15}H_{12}N_2O$ requires C, 76·25; H, 5·1; N, 6·8%).

4-Aminobiphenyl-3-carbonitrile.—Hydrolysis of 4-acetamido-3-bromobiphenyl [16] with 50% aqueous sulphuric acid followed by treatment of the free base in the manner described in the previous experiment gave the *nitrile* as pale brown prisms (45%), m.p. 143—144° (from ethanol), *m/e* 194 (M^+, base), 166, and 139; $\nu_{max.}$ 3460, 3360 (NH_2), and 2205 cm^{-1} (CN) (Found: C, 80·1; H, 5·1; N, 14·6. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·2; N, 14·4%).

5-Phenylanthranilic Acid.—(a) *From 4-aminobiphenyl-3-carbonitrile.* The nitrile was heated under reflux with aqueous 30% potassium hydroxide and an equal volume of ethanol until evolution of ammonia ceased (*ca.* 24 h). The ethanol was then distilled off and the residual solution acidified with concentrated hydrochloric acid to pH 3. After cooling, the precipitated acid was filtered off and crystallized from methanol to give prisms (85%), m.p. 200—201° (lit.,[17] 200—202°) (Found: C, 73·0; H, 5·4; N, 6·5. Calc. for $C_{13}H_{11}NO_2$: C, 73·2; H, 5·2; N, 6·6%).

(b) *From 4-acetamidobiphenyl-3-carbonitrile.* Hydrolysis of this compound under the same conditions as in method (a) was extremely slow; heating for 1 week was required before the evolution of ammonia stopped. The mixture was worked up as before (yield 80—86%).

N-(3-Carboxybiphenyl-4-yl)glycine.— 5-Phenylanthranilic acid (213 mg), chloroacetic acid (0·94 g), sodium carbonate (1·5 g), copper powder (0·1 g), and water (8 cm^3) were heated under reflux for 2 h. The hot mixture was filtered and the filtrate cooled and acidified to pH 3 with concentrated hydrochloric acid. After further cooling the product was collected, washed with water, and dried. Recrystallization from aqueous ethanol gave pale yellow *crystals* (65%), m.p. 211—213°, $\nu_{max.}$ 3380, 2900, 1720, 1670, and 1230 cm^{-1} (Found: C, 62·5; H, 5·2; N, 4·65. $C_{15}H_{13}NO_4,H_2O$ requires C, 62·3; H, 5·2; N, 4·8%).

1,3-Diacetyl-5-phenylindoxyl (4; R = Ph). A mixture of acetic anhydride (5 cm^3) and triethylamine (1 cm^3) was treated with the foregoing glycine (1 g) by heating on a steam-bath until all the solid had dissolved. The solution was then heated under reflux for a further 20 min. The solvents were removed under reduced pressure and the residue was extracted with hot petroleum (b.p. 60—80°). The extracts were boiled with charcoal, filtered, and evaporated to give needles (40%), m.p. 138—139° (from ethanol), *m/e* 293 (M^+), 251 (base), 209, and 152; $\nu_{max.}$ 1760 (NAc) and 1700 cm^{-1} (OAc); δ ($CDCl_3$) 8·5 (1H, d, *J* 8 Hz, 7-H), 7·65 (7H, m, 5-Ph, 2- and 4-H), 7·4 (1H, d, *J* 8 Hz, 6-H), and 2·6 and 2·35 (2 × 3H, s, OAc and NAc) (Found: C, 73·5; H, 5·3; N, 4·7. $C_{19}H_{15}NO_3$ requires C, 73·7; H, 5·15; N, 4·8%).

2-{1-[3-(Methoxyethyl)-4-pyridyl]ethylidene}-5-phenylindolin-3-one (E *and* Z-*Isomers*) (5; R = Ph). 1,3-Diacetyl-5-phenylindoxyl (780 mg) and 4-acetyl-3-(1-methoxyethyl)-pyridine (540 mg) were dissolved in aqueous 50% methanol

[15] B. Festy, J. Poisson, and C. Paoletti, *F.E.B.S. Letters*, 1971, **17**, 321.

[16] D. J. Byron, G. W. Gray, A. Ibbotson, and B. M. Worral, *J. Chem. Soc.*, 1963, 2256.

[17] G. Kranzlein, P. Ochwat, and K. Moldaenke, U.S.P. 2,012,569/1935.

(9 cm³) containing potassium hydroxide (1·8 g). The mixture was set aside under nitrogen. Within the first 24 h some orange crystals separated, but later green prisms also formed. After 4 days the solids were collected and washed with cold 50% aqueous methanol (yield 965 mg, 98%). The green compound, which is more soluble in most organic solvents than the orange product, is the *E*-isomer; the latter compound is the *Z*-form.

The E-*isomer* had m.p. 222—224°; *m/e* 270 (M^+), 338, 323 (base), 311, 295, and 162; $\nu_{max.}$ 3120 (NH), 1690 (CO), and 1640 cm^{-1} (C=C); δ [$CDCl_3$–5% $(CD_3)_2SO$] 8·8br (1H, s, NH), 8·74 (1H, s, 2′-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), 7·0—8·5 (9H, m, 5-Ph, 4-, 5′-, 6-, and 7-H), 4·4 (1H, two superimposed quartets, *J* 7 Hz, C*H*·CH_3), 3·23 and 3·15 (3H, 2 × s, OCH_3), 2·26 and 2·11 (3H, 2 × s, CH_3C), and 1·43 and 1·28 (3H, 2 × d, *J* 7 Hz, CH_3·CH) (Found: C, 78·0; H, 6·1; N, 7·5. $C_{24}H_{22}N_2O_2$ requires C, 77·8; H, 6·0; N, 7·6%). The orange product was not obtained free from the green isomer; consequently complete physical data are not available. A carbonyl band at 1685 cm^{-1} in the i.r. spectrum of the crude product and a chemical shift of δ 2·6 for the n.m.r. signal of an olefinic methyl group support the *Z*-assignment.

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethyl*}-5-*phenylindole* (7; R = Ph).—Compound (5; R = Ph) (*EZ*-mixture; 3·3 g) in aqueous 70% ethanol (300 cm³) was treated with sodium borohydride (*ca.* 10 g) while boiling under reflux. After *ca.* 1 h the solvents were evaporated off and the residue partitioned between chloroform and water. The chloroform layer was dried and evaporated to leave the indoline (6; R = Ph). This was dissolved in dry methanol and the solution saturated with hydrogen chloride gas; the solvent was removed and the residue extracted with a mixture of sodium hydrogen carbonate solution and chloroform. The organic layer was then separated, dried, and evaporated to give a solid which crystallized from ethanol as solvated *prisms*, m.p. 185—186°, *m/e* 356 (M^+), 324, 309 (base), and 294; $\nu_{max.}$ 3150 (NH) and 1605 cm^{-1} (C=C); δ ($CDCl_3$) 8·63 and 8·54 (1H, 2 × s, 2′-H), 8·4 (1H, m, 6′-H), 8·3br (1H, s, NH), 7·1—7·8 (9H, m, 5-Ph, 4-, 5′-, 6-, and 7-H), 6·5 (1H, s, 3-H), 4·5—4·9 [2H, two superimposed quartets, C*H*·CH_3 and C*H*(OCH_3)·CH_3], 3·7 (2H, q, *J* 7 Hz, CH_3·C*H*$_2$·OH), 3·36 (3H, 2 × s, OCH_3), 1·4—1·8 [6H, m, C*H*$_3$·CH= and C*H*$_3$·CH(OCH_3)], and 1·1 (3H, t, *J* 7 Hz, C*H*$_3$·CH_2·OH) (Found: C, 77·5; H, 7·4; N, 7·0. $C_{24}H_{24}N_2O$,CH_3CH_2OH requires C, 77·6; H, 7·5; N, 7·0%).

9-*Phenylellipticine* (9; R = Ph).—The indole (7; R = Ph) (1 g) in aqueous 60% hydrobromic acid (20 cm³) was heated under reflux until no further change was observed in the u.v. spectrum (*ca.* 5 h). The solution was then cooled and the solid which had separated collected, washed with 60% hydrobromic acid, and dried. The free base was liberated from this salt by treatment with aqueous sodium carbonate and extracted into chloroform.

The chloroform extracts yielded 9-phenylellipticine as yellow prisms (423 mg, 47%), m.p. 307—308°, *m/e* 322 (base), 307, and 162; $\nu_{max.}$ 3120 (NH) and 1600 cm^{-1} (C=C); $\lambda_{max.}$ 231 (ε 33,810), 265sh (41,860), 275sh (46,150), 299 (66,545), 349 (11,810), and 354 nm (8590) δ (CF_3·CO_2H) 9·3 (1H, m, 1-H), 8·0 (3H, m, 3-, 4-, and 10-H), 7·4 (7H, m, 9-Ph, 7- and 8-H), 292 (3H, s, 11-Me), and 2·63 (3H, s, 5-Me) (Found: C, 85·5; H, 5·7; N, 8·3%; M^+, 322·1465. $C_{23}H_{18}N_2$ requires C, 85·7; H, 5·6; N, 8·7%; *M*, 322·1470).

1,3-*Diacetyl*-5-*bromoindoxyl* (4; R = Br).—5-Bromoanthranilic acid was converted into 2-carboxy-4-bromophenylglycine by the method of Holt *et al.*[18] This compound was transformed into (4; R = Br) as described above for the phenyl analogue (4; R = Ph); yield 52%; m.p. 121—122° (lit.,[10] 123°); δ ($CDCl_3$) 8·25 (1H, d, *J* 7 Hz, 7-H), 7·61 (1H, s, 2-H), 7·58 (1H, d, *J* 2 Hz, 4-H), 7·35 (1H, 2 × d, *J* 7 and 2 Hz, 6-H), and 2·50 and 2·27 (2 × 3H, 2 × s, OAc and NAc).

5-*Bromo*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethylidene*}*indoline*-3-*one* (5; R = Br).—1,3-Diacetyl-5-bromoindoxyl was combined with the acetylpyridine (2) as described for the preparation of (5; R = Ph). At the end of 4 days, however, no solid had separated so the mixture was poured on to water containing sufficient dilute hydrochloric acid to adjust the pH to *ca.* 7. Extraction with dichloromethane afforded, after removal of the solvent, a dark coloured solid (80%), which crystallized from aqueous ethanol as dark brown rosettes, m.p. 207—208°. This compound was the *Z*-isomer; the *E*-isomer was not obtained pure.

The Z-*isomer* showed *m/e* 372/374, 340/342, 325/327 (base), 313/315, 246, and 218; $\nu_{max.}$ 1685 (CO) and 1630 cm^{-1} (C=C); δ ($CDCl_3$) 8·6 (1H, d, *J* 3 Hz, 2′-H), 8·18 (1H, 2 × d, *J* 5 and 3 Hz, 6′-H), 7·8 (1H, d, *J* 1·5 Hz, 4-H), 7·44 (1H, 2 × d, *J* 8 and 1·5 Hz, 6-H), 6·7 (1H, d, *J* 8 Hz, 7-H), 4·4 [1H, q, *J* 7 Hz, CH_3·C*H*(OCH_3)] 3·3 and 3·25 (3H, 2 × s, O*CH*$_3$), 2·70 and 2·65 (3H, 2 × s, C*H*$_3$·C=), and 1·45br and 1·40br (3H, d, *J* 7 Hz, CH_3CH(OCH_3)] (Found: C, 58·0; H, 4·5; N, 7·4. $C_{18}H_{17}BrN_2O_2$ requires C, 57·9; H, 4·6; N, 7·5%).

5-*Bromo*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (7; R = Br).—The indolin-3-one (5; R = Br) was treated with sodium borohydride in the usual way; the product reacted with hydrogen chloride to give *compound* (7; R = Br) (38%), m.p. 166—167° (from methanol), *m/e* 358/360 (M^+), 326/328, 311/313, (base) 296/298, 247, and 232; $\nu_{max.}$ 3150 (NH) and 1605 cm^{-1} (C=C); δ ($CDCl_3$) 8·45 (1H, d, *J* 9 Hz, 7-H), 8·3 (1H, d, *J* 5 Hz, 6′-H), 7·6br (1H, s, 2′-H), 7·2 (3H, m, 4-, 5′-, and 6-H), 6·3br (1H, s, 3-H), 4·6 [2H, two superimposed quartets, C*H*·CH_3 and C*H*(OCH_3)CH_2], 3·3 (3H, 2 × s, OCH_3), and 1·75 and 1·45 [6H, m, C*H*$_3$·CH= and C*H*$_3$·CH(OCH_3)] (Found: C, 59·8; H, 5·4; N, 7·6. $C_{18}H_{19}BrN_2O$ requires C, 60·2; H, 5·3; N, 7·8%).

9-*Bromoellipticine* (9; R = Br).—The indole (7; R = Br) (250 mg) was dissolved in aqueous 60% hydrobromic acid (25 cm³) and heated under reflux for 1 h. The solution was cooled and neutralized with sodium carbonate. Extraction with chloroform and evaporation of the extract left a residue which crystallized when triturated with chloroform to yield a product (185 mg) which was principally ellipticine. The mass spectrum showed molecular ions corresponding to ellipticine, *m/e* 246·1155 (calc. for $C_{17}H_{14}N_2$: 246·1157); 9-bromoellipticine, *m/e* 324·0260 (calc. for $C_{17}H_{13}BrN_2$: 324·0263); 5- or 11-demethylellipticine, *m/e* 232·0008 (calc. for $C_{16}H_{12}N_2$: 232·1000); and 5- or 11-demethyl-9-bromoellipticine, *m/e* 310·0094 (calc. for $C_{16}H_{11}BrN_2$: 310·0106). Repeated sublimation and recrystallization afforded, eventually, pure ellipticine, identical (m.p. and i.r. and u.v. spectra) with an authentic sample, but despite numerous attempts using various solvent mixtures and adsorbents we were unable to obtain satisfactory separations of the other components by column or thin-layer chromatography.

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* 1-*Oxide* (12).—3-Acetylpyridine 1-oxide[19] (4·9 g) was heated with toluene-*p*-sulphonic acid (1·1 mol. equiv.) in ethylene glycol (20 cm³) and dry benzene (400 cm³) in a Dean-Stark apparatus for 6 h. The mixture was then cooled and the benzene layer separated

[18] S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.*, 1958, **148**, 481.
[19] S. Kanno, *J. Pharm. Soc.* (*Japan*), 1952, **72**, 120.

and evaporated to give the acetal (12) as an oil. More product was isolated from the ethylene glycol layer by dilution with water and extraction with chloroform. The combined product was distilled (oil-bath temperature 200—230°) to give an oil which slowly crystallized to afford a hygroscopic solid with indefinite m.p.; $\nu_{max.}$ 2980, 2880, and 2030 cm^{-1}; δ ($CDCl_3$) 3·95 (4H, m, O·CH_2·CH_2·O) and 1·65 (3H, s, CCH_3).

The hydrochloride of this compound was prepared by treatment with chloroform saturated with hydrogen chloride, followed by removal of the solvent.

Reaction of the Acetal (12) *with Phosphoric Trichloride.*—The hydrochloride of (12) (1·66 g) was heated with phosphoric trichloride (6 cm^3) at 120° for 2 h. After cooling, the solution was poured onto aqueous 2N-potassium carbonate and ice; extraction with ether then afforded an oil (1·48 g) which partially crystallized. The mass spectrum of this product showed a molecular ion cluster (*m/e* 217/219/221; $C_9H_9Cl_2NO$) presumed to be due to compound (17); a group of ions corresponding to $C_9H_{10}ClNO_2$, probably (14) and (15); and a further cluster, *m/e* 311/413/415 ($C_{21}H_{12}Cl_3N_3$) due to the tetracycle (16).

The oil was warmed with 6N-hydrochloric acid on a water-bath for 10 min and the solution then extracted with chloroform.* The organic phase was washed with 5% sodium carbonate solution, dried, and evaporated to give an oil which crystallized on trituration with ether affording *tris-(6-chloro-3-pyridyl)benzene* (16) as pale yellow plates (80 mg), m.p. 264—266° (from acetone); $\nu_{max.}$ 1600, 1580, 1560, and 1205 cm^{-1}, $\lambda_{max.}$ 257 (ε 39,640) and 278sh nm (25,280), δ ($CDCl_3$) 8·7 (3H, d, *J* 2 Hz, 3 × 6′-H), 7·95 (3H, 2 × d, *J* 8 and 2 Hz, 3 × 4′-H), 7·75 (3H, s, benzenoid), and 7·5 (3H, d, *J* 8 Hz, 3 × 5′-H) (Found: C, 61·0; H, 3·0; N, 10·1. $C_{21}H_{12}Cl_3N_3$ requires C, 61·1; H, 2·9; N, 10·2%).

Action of Dimethylcadmium on 4-Chloropyridine-3-carbonyl Chloride.—4-Chloropyridine-3-carboxylic acid (5·3 g) was heated under reflux with thionyl chloride (80 cm^3) for 3 h. The excess of reagent was then distilled off, and last traces were removed by addition of benzene and evaporation under reduced pressure. The residue was covered with dry ether and treated with dry triethylamine after stirring for 10 h. The precipitate of triethylamine hydrochloride was removed and the filtrate treated at room temperature with an excess of dimethylcadmium in ether. The mixture was then heated under reflux for a further 3 h. After cooling, sufficient aqueous 15% ammonium chloride was added to decompose the complex and the excess of dimethylcadmium, the ether layer was separated, and the aqueous phase was extracted with ether. The combined ether layers were washed with sodium carbonate solution, dried, and evaporated to give an orange gum. This was dissolved in chloroform † and extracted with 2N-sulphuric acid. The acid extract was then basified to yield 4-chloro-*NN*-diethylpyridine-3-carboxamide (20) as an oil (400 mg), M^+ 212/214; $\nu_{max.}$ 1635 cm^{-1}; δ ($CDCl_3$) 1·08 (3H, t, *J* 7 Hz, CH_2·CH_3), 1·26 (3H, t, *J* 7 Hz, CH_2CH_3), 3·14 (2H, q, *J* 7 Hz, CH_2·CH_3), 3·60 (2H, q, *J* 7 Hz, CH_2·CH_3), 7·35 (1H, d, *J* 5 Hz, 5-H), 8·45 (1H, s, 2-H), and 8·50 (1H, d, *J* 5 Hz, 6-H). The oil decomposed when attempts were made to distil it.

1,1-Dimethylfuro[3,4-c]pyridin-3(1H)-one (22).—Pyridine-3,4-dicarboxylic acid (3·8 g) was treated with thionyl chloride (20 cm^3) in dimethylformamide (2 g) and the mixture was heated under reflux for 2½ h, then set aside at room temperature overnight. Solvent and reagent were removed and the residue was treated with a five-fold excess of dimethylcadmium in ether. Benzene was then introduced, the ether was distilled off, and the mixture was kept at 36—38° for 3½ h. After cooling, ammonium chloride (20 g) in water (100 cm^3) and concentrated hydrochloric acid (20 cm^3) was added slowly; the aqueous layer was then separated, basified with sodium carbonate, and extracted with chloroform. Removal of the chloroform yielded crude (22) as a red oil which gradually crystallized on trituration with ether. The product (200 mg) crystallized from ether as yellow needles, m.p. 152—155° (lit.,[10] 160—161°); $\nu_{max.}$ 1760, 1608, 1300, and 1040 cm^{-1}; δ ($CDCl_3$) 9·10 (1H, s, 4-H), 8·84 (1H, d, *J* 6 Hz, 6-H), 7·40 (1H, d, *J* 6 Hz, 7-H), and 1·65 (6H, s, CMe_2) (Found: C, 66·0; H, 5·7. Calc. for $C_9H_9NO_2$: C, 66·2; H, 5·6%).

3-Acetyl-1,4-dihydro-1-(4-nitrobenzyl)pyridine-4-carbonitrile (27).—3-Acetyl-1-(4-nitrobenzyl)pyridinium bromide (3 g) in water (80 cm) was added dropwise during 30 min to a vigorously stirred solution of potassium cyanide (5·8 g) in water (20 cm^3). After a further 30 min, an unstable yellow solid formed; this was filtered off; m.p. 110—130° (decomp.); $\nu_{max.}$ 2230, 1680, 1640, 1580, 1520, and 1340 cm^{-1}; δ [$(CD_3)_2SO$] 8·65 (2H, d, *J* 9 Hz, 3′- and 5′-H), 8·24 (1H, s, 2-H), 7·96 (2H, d, *J* 9 Hz, 2′- and 6′-H), 6·70 (1H, d, *J* 8 Hz, 6-H), 5·25 (1H, 2 × d, *J* 8 and 5 Hz, 5-H), 5·02 (2H, s, CH_2Ar), 4·72 (1H, d, *J* 5 Hz, 4-H), and 2·32 (3H, s, Ac).

Reaction of the Nitrile (27) *with Hydrochloric Acid.* The dihydropyridine (27) (114 mg) in chloroform (7 cm^3) was treated with aqueous 2N-hydrochloric acid (10 cm^3) and the mixture heated at 55—60° for 1 h. The aqueous phase was separated, neutralized with sodium carbonate, and extracted with chloroform to yield a gum which crystallized from ethanol to give *5-acetyl-1,2,3,4-tetrahydro-2-hydroxy-1-(4-nitrobenzyl)pyridine-4-carboxamide* (28) as pale yellow prisms, m.p. 179—180° (90·6 mg), *m/e* 319 (M^+) and 275 (base); $\nu_{max.}$ 3300, 1660, 1620, 1570, 1510, 1345, and 1060 cm^{-1}; δ [$(CD_3)_2SO$] 8·22 (2H, d, *J* 8 Hz, 3′- and 5′-H), 7·85 (1H, s, 6-H), 7·58 (2H, d, *J* 8 Hz, 2′- and 6′-H), 7·5br (1H, s, OH), 7·36br (2H, d, *J* 14 Hz, $CONH_2$), 4·76 (2H, s, CH_2Ar), 4·52 (1H, d, *J* 10 Hz, CHOH), 3·65 (1H, 2 × d, *J* 6 and 2 Hz, 4-H), 2·20 and 1·82 (2H, m, 3-H_2), and 2·12 (3H, s, Ac) (Found: C, 56·3; H, 5·4; N, 13·0. $C_{15}H_{17}N_3O_5$ requires C, 56·4; H, 5·4; N, 13·2%).

Reaction between 3-Acetylpyridine and Hydroxylamine-O-sulphonic Acid.—3-Acetylpyridine (1·94 g) in water (4 cm^3) was added to a solution of hydroxylamine-*O*-sulphonic acid (3·62 g) and potassium hydroxide (1·79 g) in water (6·4 cm^3) maintained below 0°. The temperature was raised to 70° for 4 h, and the solution was then cooled and basified with sodium carbonate (2·2 g) in water (3·3 cm^3). After ½ h the

* The aqueous phase was basified and extracted with chloroform to give an oil (30 mg), the ^1H n.m.r. spectrum of which showed it to be 3-acetyl-2-chloropyridine [δ ($CDCl_3$) 8·50 (1H, m, 6-H), 7·92 (1H, m, 5-H), 7·35 (1H, m, 4-H), and 2·70 (3H, s, Ac)] contaminated with *ca.* 5% of the 6-chloro-isomer. Assignment of this latter structure rests upon the fact that only one α-pyridine proton signal is observed [δ 8·95 (d *J* 2 Hz)]; the remainder of the spectrum is difficult to assign because of the low intensity of the signals, apart from that due to the acetyl protons which appears as a singlet (δ 2·62).

† The chloroform layer was dried and evaporated to give, as a yellow solid, *1,3-bis-(4-chloro-3-pyridyl)-3-hydroxyprop-2-en-1-one* (21), which crystallized on trituration with acetone as yellow plates, m.p. 239—241° (from acetone), M^+ 294/296/298, $\nu_{max.}$ 3160, 1580, 1105, and 1010 cm^{-1}; δ (CF_3·CO_2H) 9·42 (2H, d, *J* 2 Hz, 2 × 2′-H), 9·16 (2H, 2 × d, *J* 8 and 2 Hz, 2 × 6′-H), 8·2 (2H, d, *J* 8 Hz, 2 × 5′-H), and 7·34 (1H, s, =CH–) (Found: C, 53·0; H, 3·0; N, 9·4 $C_{13}H_8Cl_2N_2O_2$ requires C, 52·9; H, 2·7; N, 9·5%).

mixture was acidified with concentrated hydrochloric acid and filtered, and the filtrate was evaporated. The residue was treated with methanol and the mixture filtered. On concentration, the methanolic filtrate yielded a crystalline solid. Without purification, this was treated with acetic anhydride (16 cm^3) during 5 h; the excess of reagent was then removed under reduced pressure to afford a brown oil which was chromatographed on neutral aluminia (100 g) with 2% methanol in dichloromethane as eluant. Fifty fractions (30 cm^3) were collected: t.l.c. indicated that fractions 3—34 contained the same material and on combination and evaporation these yielded a solid which crystallized from di-isopropyl ether–petroleum (b.p. 60—80°) as pale yellow prisms (0·99 g), m.p. 116—117°. This material was identical with the authentic oxime of 3-acetylpyridine (lit.,[20] m.p. 113°) (from di-isopropyl ether), but was contaminated with a trace of its *O*-acetate.

The remaining fractions were combined and evaporated to yield 3-(1-*hydroxyiminoethyl*)*pyridine* N-*acetylimidine* (31) (30 mg), m.p. 188—190° (from acetone), M^+ 193, $\nu_{max.}$ 3400—2500, 1560, and 1030 cm^{-1}, δ [$(CD_3)_2SO$] 8·90 (1H, d, *J* 2 Hz, 2-H), 8·70 (1H, m, 6-H), 8·38 (1H, m, 4-H), 7·9 (1H, m, 5-H), 2·20 (3H, s, Ac), and 1·85 (3H, s, CH_3C) (Found: C, 56·0; H, 6·1; N, 22·05. $C_9H_{11}N_3O_2$ requires C, 55·95; H, 5·7; N, 21·75%).

1-*Amino*-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridinium Mesitylenesulphonate*.— 3-(2-Methyl-1,3-dioxolan-2-yl)pyridine (15·6 g) in dichloromethane (42 cm^3) was cooled to 0° and *O*-mesitylsulphonylhydroxylamine (20·4 g) in dichloromethane (40 cm^3) was added. After stirring at room temperature for 30 min, the solution was diluted with diethyl ether (800 cm^3) and again cooled to 0°. After a few minutes, the crystalline product was collected (33·8 g, 94·0%); m.p. 118—119°; $\nu_{max.}$ 3210, 3130, and 1190 cm^{-1}; δ [$(CD_3)_2SO$] 9·15 (1H, s, 2-H), 9·10 (1H, d, *J* 8 Hz, 6-H), 8·95br (2H, s, NH_2), 8·50 (1H, d, *J* 9 Hz, 4-H), 8·35 (1H, q, *J* 8 and 9 Hz, 5-H), 7·03 (2H, s, benzenoid), 4·3—3·8 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 2·50 (6H, s, 2 × CH_3), 2·49 (3H. s, CH_3), and 1·70 (3H, s, CH_3).

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* N-*Acetylimide* (32).—The product from the previous reaction was dissolved in water (100 cm^3) and treated with acetic anhydride (200 cm^3), previously cooled to 5°, and then dropwise with aqueous 30% sodium hydroxide (150 cm^3). The mixture was then poured into aqueous potassium carbonate (100 g in 900 cm^3) and stirred with chloroform (100 cm^3). A colourless precipitate was removed and the aqueous phase separated and extracted with chloroform (100 cm^3). The chloroform layers were combined, dried, and evaporated to give (32) as an amber-coloured oil which slowly crystallized to afford a hygroscopic solid (19·2 g, 98%), *m/e* 222 (M^+) and 207 (base); $\nu_{max.}$ 1570 cm, δ ($CDCl_4$) 9·0 (2H, m, 2- and 6-H), 8·35 (1H, d, *J* 8 Hz, 4-H), 7·95 (1H, q, *J* 8 and 7 Hz, 5-H), 4·40—3·90 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 2·13 (3H, s, Ac), and 1·72 (3H, s, CH_3).

1-(N-*Methylacetamido*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-*pyridinium Iodide* (33).—The pyridine (32) (15·1 g) was treated with methyl iodide (150 cm^3) at reflux during 45 min. Removal of the excess of reagent afforded a yellow solid (98%), m.p. 176—177° (from ethanol).

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine*-4-*carbonitrile* (34).—The salt (33) (24 g) in water (56 cm^3) was warmed to 20—22° and treated with ammonium chloride (7·0 g) and potassium cyanide (5·6 g) in water (10 cm^3). After 1 h the mixture was extracted with chloroform to yield an oil, which was stirred in ethanol solution and irradiated with 'soft' u.v. light for 15 min. The solvent was removed under reduced pressure to give (34) as a solid which crystallized from ethyl acetate as *needles* (10·2 g, 81·5%), m.p. 68—69°, *m/e* 190 (M^+), 175 (base), 131, and 87, δ [$(CD_3)_2SO$] 1·70 (3H, s, CH_3C), 3·9 (4H, m, $CH_2{\cdot}CH_2$), 7·8 (1H, d, *J* 5 Hz, 5-H), 8·7 (1H, d, *J* 5 Hz, 6-H), and 8·8 (1H, s, 2-H) (Found: C, 63·2; H, 5·3; N, 14·7. $C_{10}H_{10}N_2O_2$ requires C, 63·15; H, 5·3; N, 14·7%).

4-*Acetyl*-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* (36).—The nitrile (34) (1·0 g) in ether (30 cm^3) was added slowly to a solution of methyl-lithium (1·2 mol. equiv.) in ether at −10 to −15° under nitrogen. Stirring was maintained for a further 30 min, and then ice–water (40 cm^3) was introduced followed by ammonium chloride (1·0 g) in water (10 cm^3). The ethereal layer was removed, dried, and evaporated to give a small amount of starting material. Extraction of the aqueous phase with chloroform gave an oil which slowly crystallized to afford prisms of 4-(1-*iminoethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* (35), m.p. 85—86° (from ether) (0·97 g, 89·5%); $\nu_{max.}$ 1640 and 1590 cm^{-1}; δ ($CDCl_3$) 1·8 (3H, s, CH_3C), 2·40 (3H, s, $CH_3{\cdot}C{=}N$), 3·7—4·1 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·01 (1H, d, *J* 5·5 Hz, 5-H), 8·55 (1H, d, *J* 5·5 Hz, 6-H), and 8·82 (1H, s, 2-H) (Found: C, 64·0; H, 6·7; N, 13·3. $C_{11}H_{14}N_2O_2$ requires C, 64·1; H, 6·8; N, 13·6%).

Treatment of the imine (5·7 g) with aqueous 20% acetic acid (160 cm^3) on a steam-bath for 30 min, followed by basification (K_2CO_3) and extraction with chloroform afforded the 4-acetyl derivative (36) as prisms (5·3 g, 94·5%), m.p. 49—50° [from petroleum (b.p. 60—80°)]; $\nu_{max.}$ 2980, 2890, 1705, and 1030 cm^{-1}; $\lambda_{max.}$ 263 nm (ε 2490); δ ($CDCl_3$) 1·8 (3H, s, CH_3C), 2·5 (3H, s, CH_3CO), 3·8 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·0 (1H, d, *J* 5 Hz, 5-H), 8·55 (1H, d, *J* 5 Hz, 6-H), and 8·75 (1H, s, 2-H) (Found: C, 63·7; H, 6·4; N, 6·7. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%).

3,4-*Diacetylpyridine* (10).—Hydrolysis of the imine (35), this time with aqueous 20% hydrochloric acid at 100° for 30 min, gave 3,4-*diacetylpyridine* (96%), m.p. 42—44° [from petroleum (b.p. 40—60°)], $\lambda_{max.}$ 227 (ε 5740) and 275 nm (2420); $\nu_{max.}$ 1710br and 1590 cm^{-1}; δ ($CDCl_3$) 2·50 (3H, s, Ac), 2·64 (3H, s, Ac), 7·32 (1H, d, *J* 6 Hz, 5-H), 8·85 (1H, d, *J* 6 Hz, 6-H), and 9·05 (1H, s, 2-H) (Found: C, 66·0; H, 5·7; N, 8·9. $C_9H_9NO_2$ requires C, 66·2; H, 5·6; N, 8·6%).

Reaction between 3,4-*Diacetylpyridine and Ethane*-1,2-*diol*.—3,4-Diacetylpyridine (1·6 g) in dry benzene (50 cm^3) containing toluene-*p*-sulphonic acid (1·15 mol. excess) and ethane-1,2-diol (5 cm^3) was heated in a Dean-Stark apparatus for 12 h. Removal of the solvents gave a red oil which was chromatographed upon basic alumina (50 g), with ether as eluant. Thirty fractions (50 cm^3) were collected. Fractions 1—7 yielded a white crystalline solid (64 mg), m.p. 141—142 [from petroleum (b.p. 60—80°)], identified as 5,7,8,10-*tetrahydro*-5,10-*dimethyl*-5,10-*epoxy*[1,4]*dioxepino*-[6,7-c]*pyridine* (37), $\lambda_{max.}$ 260 (ε 1750) and 265sh nm (1520); δ ($CDCl_3$) 1·80 (3H, s, CH_3C), 1·83 (3H, s, CH_3C), 3·3 and 3·85 (2 × 2H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·25 (1H, m, 4-H), and 8·62 (2H, m, 1- and 3-H), *m/e* 207 (M^+) and 147 (base) (Found: C, 63·8; H, 6·8; N, 7·2. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%). Fractions 23—30 gave an oil (70 mg) the ^1H n.m.r. spectrum of which indicated the presence of a mixture of the acetals (36) and (38) (*ca.* 3 : 1).

3-[1-(*Tetrahydropyran*-2-*yloxy*)*ethyl*]*pyridine*.—The hydrochloride of 3-(1-hydroxyethyl)pyridine (32·4 g) was treated with 2,3-dihydropyran (3 mol. equiv.) in dimethylformamide (200 cm^3), and dry hydrogen chloride was then bubbled

[20] F. B. La Forge, *J. Amer. Chem. Soc.*, 1928, **50**, 2477.

through the solution for 10 min. The mixture was set aside for 5 days. The solvent was removed under reduced pressure and the residue was treated with a mixture of ether and aqueous 10% sodium carbonate. The organic layer was then separated, washed with water, dried, and evaporated to give the required ether as an oil (37·8 g, 90·0%), b.p. 100—102° at 0·65 mmHg. This product was converted, by a series of steps similar to those described previously for (36), into 4-acetyl-3-[1-(tetrahydropyran-2-yloxy)ethyl]pyridine (39), obtained as an oil after chromatography upon alumina and elution with ether [yield from 3-(1-hydroxyethyl)-pyridine, 65%]; M^+ 249; $\nu_{max.}$ 1700, 1580, and 1255 cm^{-1}; δ ($CDCl_3$) 9·04 (1H, 2 × s, 2-H), 8·75 (1H, m, 6-H), 7·4 (1H, m, 5-H), 5·3 (1H, q, C*H*·CH_3), 3·96—3·31 (3H, m, CHO and CH_2O), 2·63 (3H, s, Ac), and 1·8—1·3 (9H, m, CH_2·CH_2·CH_2 and $CHCH_3$) (Found: C, 67·3; H, 7·5; N, 5·8. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%).

1,3-*Dihydro*-1,3-*dimethylfuro*[3,4-c]*pyridin*-1-*ol* (41).—The 4-acetylpyridine (39) (1·4 g) in dilute hydrochloric acid (20 cm^3) was warmed on a steam-bath for 10 min. The solution was then basified with sodium carbonate and extracted with chloroform; removal of the solvent gave (41) as an *oil* (1·0 g). This was purified by repeated chromatography upon alumina (elution with ether); *m/e* 165 (M^+) and 150 (base); $\nu_{max.}$ (film) *ca.* 3300 and 1605 cm^{-1}; δ ($CDCl_3$) 8·44 (1H, two overlapping d, 4-H), 8·34 (1H, m, 6-H), 7·3 (1H, m, 7-H), 5·36 (1H, two overlapping q, C*H*CH_3), 1·78 and 1·78 (3H, two s, CH_3C), 1·50 (3H, two overlapping d, C*H*$_3$CH), and 4·92br (1H, s, OH); $\lambda_{max.}$ 255sh (ε 1130), 260 (1320), and 266sh nm (1130) (Found: C, 65·0; H, 6·3; N, 8·2. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5%).

The isomeric 3-*ol* (42) was obtained by reduction of (36) with sodium borohydride to give 4-(1-hydroxyethyl)-3-(2-methyl-1,3-dioxolan-2-yl)pyridine [m.p. 84·6°; $\nu_{max.}$ 3400 cm^{-1}; δ ($CDCl_3$) 8·64 (1H, s, 2-H), 8·45 (1H, d, *J* 5 Hz, 6-H), 7·55 (1H, d, *J* 5 Hz, 5-H), 5·46 (1H, q, *J* 5 Hz, CH_3CH), 4·1—3·7 (4H, m, O·CH_2·CH_2·O), 1·65 (3H, s, Ac), and 1·42 (3H, d, *J* 5 Hz, C*H*$_3$CH)] followed by treatment of this with 6N-hydrochloric acid at 100° for 10 min. The product (42), an oil, *m/e* 165 (M^+), 150, and 147 (base); $\nu_{max.}$ (film) *ca.* 3300 cm^{-1}, was not completely characterized.

Reaction between 1,3-*Diacetylindoxyl and* 3,4-*Diacetylpyridine*.—1,3-Diacetylindoxyl (1·2 g) and 3,4-diacetylpyridine (0·89 g) in deoxygenated methanol (10 cm^3) were treated with potassium hydroxide (3·5 g) in deoxygenated water (10 cm^3) under nitrogen. After 3 days at room temperature, the solution was poured onto ice and aqueous 10% acetic acid; it was then basified with sodium carbonate and extracted with chloroform, and the extracts were evaporated to yield a deep red oil. This was chromatographed on alumina (elution with benzene–chloroform mixtures) and the major fraction (650 mg) was evaporated. The residue was triturated with ethanol to give 2-(3-*methylcyclopenta*[c]*pyridin*-1-*ylidene*)*indolin*-3-*one* (40) as red prisms. This product does not have a definite m.p., but begins to darken at *ca.* 290°; *m/e* 260 (M^+, base) and 245; $\lambda_{max.}$ 229 (ε 8230), 240 (8110), 290 (8790), 336 (6760), 356sh (4510), 542 (6310), and 612 nm (3610); $\nu_{max.}$ 1690, 1630, 1610, and 1600 cm^{-1}; δ (CF_3·CO_2H) 9·2 (1H, d, *J* 7 Hz), 8·6—8·45 (2H, m), 8·0—7·6 (4H, m), 7·4—7·1 (3H, m), and 2·46 (3H, s) (Found: C, 78·4; H, 4·6; N, 10·8. $C_{17}H_{12}O_2$ requires C, 78·4; H, 4·65; N, 10·8%).

(E)- *and* (Z)-2-{1-{3-[1-(*Tetrahydropyran*-2-*yloxy*)*ethyl*]-4-*pyridyl*}*ethylidene*}*indolin*-3-*one* [(43) *and isomer*].—1,3-Diacetylindoxyl (750 mg) and (39) (860 mg) in deoxygenated methanol (6·5 cm^3) were treated with potassium hydroxide (2·5 g) in deoxygenated water (6·5 cm^3) and the mixture was stored for 4 days under nitrogen. The solid product was collected under nitrogen to yield the mixed isomers (0·93 g, 74·5%), *m/e* 364 (M^+), 280, and 247 (base); $\lambda_{max.}$ 239 (ε 21,210), 264 (32,270), 296sh (14,440), and 463 nm (7447). This material was not purified further.

(E)- *and* (Z)-5-*Acetamido*-2-{1-{3-[1-(*tetrahydropyran*-2-*yloxy*)*ethyl*]-4-*pyridyl*}*ethylidene*}*indolin*-3-*one* [(44) *and isomer*].—5-Acetamido-1,3-diacetylindoxyl was treated with the acetylpyridine (39) as described in the previous experiment. However, in this case the mixture was stored at 15—16° for 7 days prior to work-up. The product was a mixture of the required isomers plus some unacetylated materials; consequently it was dissolved in ethanol and treated with an excess of acetic anhydride. After shaking at room temperature for 10 min, the excess of reagent was decomposed with ice–water and the mixture basified with potassium carbonate. Chloroform extraction gave (44) and its isomer as a red solid (80·0%), M^+ 421; $\lambda_{max.}$ 266 (ε 14,000) and 486 nm (4600).

2-{1-[3-(1-*Hydroxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (49).—The mixture of indolinone (43) and its *Z*-isomer (300 mg) in aqueous 20% ethanol (20 cm^3) was heated at reflux under nitrogen and treated with sodium borohydride (500 mg) in small portions. After 1 h the solvent was removed and the residue partitioned between chloroform and water. The organic phase was dried, treated with charcoal, and evaporated to give the indolin-3-ol (47) as a greenish gum; this was dissolved in chloroform and the solution saturated with hydrogen chloride, then washed with sodium carbonate solution, dried, and evaporated to yield (49) as a *solid* (217 mg, 72·2%), m.p. 208—210° (from ethanol); *m/e* 266 (M^+) and 233 (base); $\lambda_{max.}$ 221 (ε 50,210), 265sh (12,290), 270 (12,640), 284 (11,410), and 293 nm (9830); $\nu_{max.}$ 3330, 3100, and 1600 cm^{-1}; δ [$(CD_3)_2SO$] 8·52 (1H, s, 2′-H), 8·24 (1H, d, *J* 5 Hz, 6′-H), 7·4—6·8 (5H, m, 4-, 5-, 6-, 7-, and 5′-H), 6·12br (1H, s, 3-H), 5·3br (1H, s, OH), 5·15 (1H, m, CH_3CHO), 4·62 (1H, q, *J* 6 Hz, CH_3CH), 1·62 (3H, d, *J* 8 Hz, CH_3CHO), and 1·38 (3H, d, *J* 6 Hz, CH_3CH) (Found: C, 76·6; H, 6·8; N, 10·3. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%).

5-*Acetamido*-2-{1-[3-(1-*hydroxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (50).—This product, pale yellow micro-crystals, m.p. 140—150°,* was obtained from (44) and its *Z*-isomer as described in the previous experiment; yield 75%; *m/e* 323 (M^+) and 290 (base); $\lambda_{max.}$ 242 (ε 22,200), 300 (4000), and 311sh nm (2600); $\nu_{max.}$ 3380br, 1660br, and 1600 cm^{-1}; δ [$(CD_3)_2SO$] 8·64br (1H, s, 2′-H), 8·35 (1H, m, 6′-H), 7·75 (1H, s, 4-H), *ca.* 7·2 (3H, m, 6-, 7-, and 5′-H), 6·1br (1H, s, 3-H), 5·33 (1H, m, OH), 5·2 (1H, m, CH_3CHO), 4·6 (1H, 2 × q, CH_3CH), 1·6 (3H, d, *J* 6 Hz, C*H*$_3$CHO), and 1·4 (3H, 2 × d, C*H*$_3$CH) (Found: C, 70·8; H, 6·5; N, 12·6. $C_{19}H_{21}N_3O_2$ requires C, 70·6; H, 6·6; N, 13·0%).

1,3-*Dihydro*-1-(*indol*-2-*yl*)-1,3-*dimethylfuro*[3,4-c]*pyridine* (46).—The mixed indolines [(43) and its *Z*-isomer] (300 mg) in aqueous 20% ethanol (20 cm^3) were treated with sodium borohydride (300 mg). The mixture was then warmed on a water bath for 30 min. The solvent was removed to afford a gum which was dissolved in methanol and saturated with hydrogen chloride. Removal of the solvent, basification of the residue with aqueous sodium carbonate, and extraction with chloroform gave a sticky solid; this was chromatographed on alumina [elution with 1 : 1 petroleum (b.p. 60—80°)–ether] to yield (46) as a cream-coloured *solid*, m.p. 178°

* Mixture of diastereoisomers.

(from benzene); *m/e* 264 (M^+) and 249 (base); $\lambda_{max.}$ 220 (ε 21,600), 268 (5800), 284 (4970), and 293 nm (4200); $\nu_{max.}$ 1595 cm^{-1}; δ ($CDCl_3$) 1·62 (3H, d, *J* 6 Hz, CH_3CH), 1·95 (CH, s, CH_3C), 5·4 (1H, q, *J* 6 Hz, CH_3CH), 6·20 (1H, d, *J* 2 Hz, 3′-H), 6·95—7·60 (5H, m, 4′-, 5′-, 6′-, 7′-, and 7-H), 8·35 (1H, s, 4-H), and 8·45 (1H, d, *J* 6 Hz, 6-H) (Found: C, 77·4; H, 5·9; N, 10·3. $C_{17}H_{16}N_2O$ requires C, 77·25; H, 6·1; N, 10·6%).

Ellipticine.—The indole (49) (207 mg) in dry dimethyl sulphoxide (1·75 cm^3) was treated with acetic anhydride (1·1 cm^3) and the solution stirred at room temperature for 2 days. The mixture was then poured into water (50 cm^3) and treated with an excess of potassium carbonate. A yellow solid which gradually formed was collected, dried, and washed with benzene to yield ellipticine (130 mg), m.p. and mixed m.p. 309—312° (lit.,[1] 309—313°) (Found: C, 83·0; H, 5·6; N, 11·2. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%).

When the indole (49) (30 mg) in dichloromethane (2 cm^3) was stirred with active manganese dioxide (300 mg) for 12 h, a yellow solution was obtained. Filtration and evaporaton gave mainly starting material, but extraction of the manganese dioxide with hot ethanol afforded a small quantity (3 mg) of ellipticine. Similarly, with boron trifluoride in ether at reflux for 1 h, (49) gave a yellow gum which contained traces of ellipticine. Repetition of this reaction, but for longer periods, gave complex mixtures; at room temperature only starting material was obtained.

With phosphoric trichloride in pyridine at room temperature, (49) gave 5,11-dihydroellipticine. Particularly in the presence of aqueous acid or during chromatography on silica, this material was gradually oxidized to ellipticine. The total yield of the latter product, however, was poor (15—20%) and we were unable to obtain satisfactory analytical data for the dihydro-compound.

9-Acetamidoellipticine (9; R = NHAc).—When the indole (50) was treated with dimethyl sulphoxide and acetic anhydride as in the previous experiment, 9-acetamidoellipticine, m.p. 245—250° (decomp.) (yellow needles from ethanol), was obtained (65·2%); *m/e* 303 (M^+, base) and 261; $\lambda_{max.}$ 225 (ε 6460), 257 (10,200), 268sh (10,920), 277 (13,040), 298 (18,620), 308sh (12,040), 339 (2480), 354 (1990), and 412 nm (1650); $\nu_{max.}$ 1660 and 1600 cm^{-1}; δ ($CF_3{\cdot}CO_2H$) 9·75br (2H, s, 1- and 3-H), 8·65—8·2 (3H, m, 7-, 8-, and 10-H), 7·75 (1H, s, 4-H), 3·40 (3H, s, 11-CH_3), 29·5 (3H, s, 5-CH_3), and 2·68 (3H, s, NHAc) (Found: C, 75·0; H, 5·6; N, 13·9. $C_{19}H_{17}N_3O$ requires C, 75·2; H, 5·65; N, 13·85%).

1′,4′-Dihydro-1′,4′-dimethylspiro{indoline-2,3′-pyrano[3,4-c]pyridin}-3-one (52).—The indole (49) (50 mg) in glacial acetic acid (1 cm^3) containing potassium dichromate (40 mg) and water (0·5 cm^3) was heated at 100° for 1 h and then poured onto 2N-sodium carbonate solution to yield a gum. This was extracted into chloroform; the extract was washed with water, dried, and evaporated and the product crystallized on trituration with acetone as pale yellow *needles* (5 mg), m.p. 244—246° (from acetone); *m/e* 280 (M^+) and 252 (base); $\nu_{max.}$ 1710 cm^{-1}; $\lambda_{max.}$ 236 (ε 18,500), 262 (5650), and 410 nm (2330); δ [$(CD_3)_2SO$] 0·98 (3H, d, *J* 3·5 Hz, CH_3CH), 1·55 (3H, d, *J* 3·7 Hz, CH_3CHO), 3·4 (1H, q, *J* 3·5 Hz, CH_3CH), 5·1 (1H, q, *J* 3·7 Hz, CH_3CHO), *ca.* 6·8—7·2 (5H, m, 5′-H and benzenoid protons), 7·8 (1H, s, NH), and 8·5br (2H, s, 6′- and 8′-H) (Found: C, 72·6; H, 5·9; N, 9·8. $C_{17}H_{16}N_2O_2$ requires C, 72·8; H, 5·75; N, 10·0%).

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A Simple Synthesis of Ellipticine and 11-Demethylellipticine

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A Simple Synthesis of Ellipticine and 11-Demethylellipticine

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Summary A new synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) is described which involves a minimum of steps and very mild reaction conditions.

DURING the last three years no less than five syntheses of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) have been described.[1] This interest has been stimulated by reports of the potentially useful anticancer activity of ellipticine and some of its derivatives.[2]

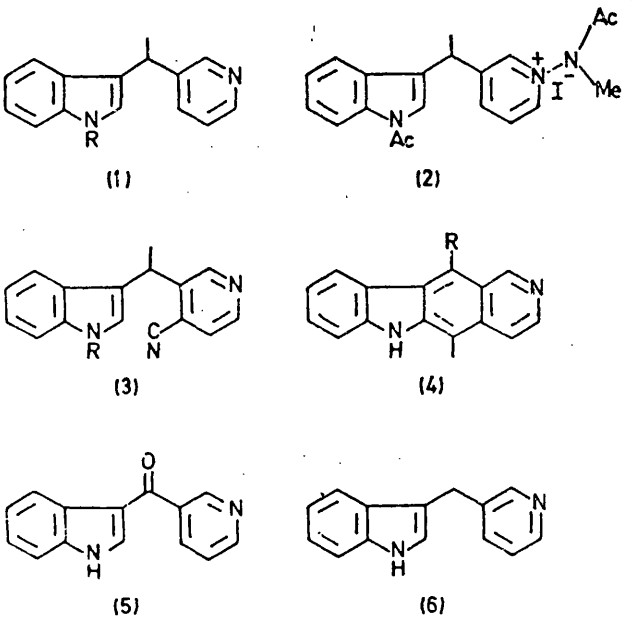
Although the new work represents a considerable advance on earlier studies,[3] as general methods all the syntheses have disadvantages either in the number of stages employed or in the severe conditions involved.

We now report a simple preparation of ellipticine (**4**, R = Me) and 11-demethylellipticine (**4**, R = H) which requires only very mild conditions and should provide an efficient general synthesis of 6*H*-pyrido[4,3-*b*]carbazoles.

Indolyl magnesium bromide is first combined with 3-(1-chloroethyl)pyridine[1d] to give 3-[1-(3-pyridyl)ethyl]-indole (**1**, R = H), m.p. 73—74 °C † (50%). The *N*(*a*)-acetyl derivative (**1**, R = Ac), m.p. 123—124 °C, is then treated in turn with *O*-mesitylsulphonylhydroxylamine, acetic anhydride and methyl iodide to give the salt (**2**), yield 75% overall; this, without purification, is treated with potassium cyanide and ammonium chloride[1e] to yield the nitrile (**3**, R = Ac) as an oil (98%). Purification and de-*N*-acetylation is effected by elution through a short column packed with basic alumina using chloroform as solvent to give (**3**, R = H), m.p. 118—119 °C (95%).

This product is treated with methyl lithium and the intermediate imine hydrolysed directly with 20% acetic acid in water (see ref. 1e) to form ellipticine (identical in m.p., i.r. spectrum, and chromatographic behaviour with an authentic specimen).[1d] Overall yield from (**1**, R = H) is 25—30%.

11-Demethylellipticine, m.p. 275—277 °C,[4] was obtained by a repetition of the above sequence using 3-(3-pyridylmethyl)indole (**6**), m.p. 157—158 °C, in place of (**1**, R = H).‡ The required starting material may be obtained from indolyl magnesium bromide and nicotinoyl chloride, followed by reduction of the product ketone (**5**), m.p. 250—251 °C with sodium borohydride, or less advantageous directly from indolyl magnesium bromide and 3-pyridylmethyl chloride. The best yield of 11-demethylellipticine from (**6**) was 28%.



(*Received, 24th March* 1975; *Com.* 357.)

† Satisfactory analytical data are available for all compounds described.

‡ We thank Miss Myra McCartney for this experiment.

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PARVINE, A NEW ANGUSTINE-TYPE ALKALOID FROM *NAUCLEA PARVA*

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PARVINE, A NEW ANGUSTINE-TYPE ALKALOID FROM *NAUCLEA PARVA**

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(*Revised received* 21 *May* 1975)

Key Word Index—*Nauclea parva*; Rubiaceae; corynanthé-type alkaloid; parvine.

Abstract—The bark of *Nauclea parva* contains several alkaloids. the most abundant of which, parvine, is of the corynanthé-type. The proof of structure of this alkaloid is given and its synthesis from harmalan and nicotinoyl chloride is described.

INTRODUCTION

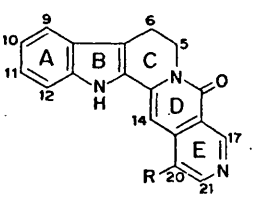
The genus *Nauclea* L. (*Sarcocephalus* Afzel ex R.Br.) of the family Rubiaceae is widely distributed in tropical regions yet, prior to the studies of McLean and his co-workers [1a–e] on *N. diderrichii*, little phytochemical work had been conducted upon members of this group. From this plant McLean has isolated a wide variety of alkaloids including simple β-carbolines, pyridines, indole pyridines and glycosidic alkaloids and recently a British group [2] have shown that pyridino-indolo-quinolizidone structures occur in the leaves of *N. coadunata*.

We now report upon the structure and synthesis of parvine the major alkaloid of *N. parva* Merrill (syn. *Sarcocephalus parvus*), a small tree indigenous to Sarawak.

RESULTS

The bark of *N. parva* contains a number of alkaloids, but individual compounds are present in very low concentrations; thus the most abundant alkaloid, parvine, represents only 0·001% of an air dried sample.

Parvine ($C_{18}H_{13}N_3O$) is an orange coloured cystalline solid which has an UV spectrum, λ_{max} (ε) nm 222 (32,356), 252 (25,740), 374 (36,480) and 392 (37,500), very similar to that of angustoline (1), λ_{max} (ε) nm 221 (30,900), 251 (23,440), 289 (13,490), 308 (8,710), 375 (38,900) and 395 (39,810), an alkaloid first isolated from an Apocynaceous plant *Strychnos angustiflora* Benth [3]. Both parvine and angustoline show bands at 1650 cm^{-1} in the IR spectra and on this basis we allocated, provisionally, structure (2) to parvine.

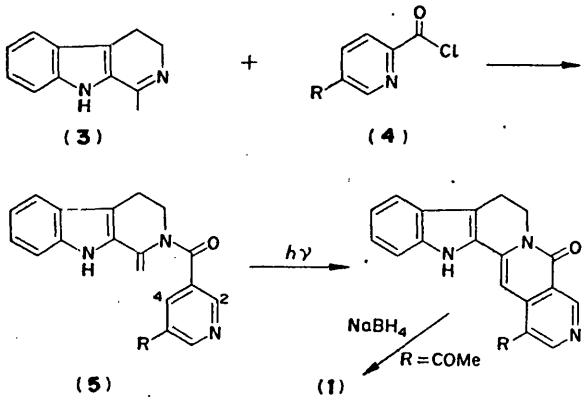


(1) R = MeCH(OH)–
(2) R = H

Parvine is very insoluble in most solvents, so that it was necessary to determine its PMR spectrum in trifluoroacetic acid: most of the features of this spectrum (see experimental) are in accord with structure (2), but because of N-protonation in this solvent and consequential coupling with the adjacent H atoms, the position of the N atom in ring E was not established with certainty. Furthermore, because of the very small amount of material available the preparation of suitable derivatives to overcome this problem was not possible.

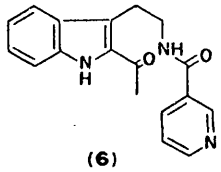
* Since going to press Prof. J. L. Pousset has isolated from *Nauclea latifolia* an alkaloid nauclefine which is identical with parvine (1975) *Phytochemistry* **14**, 1407.

(±)-Angustoline has recently been synthesised [4] by the following route:



In the penultimate step two products might arise through cyclisation of the exocyclic $-CH_2-$ group of (5, R=COMe) with either C_2 or C_4 of the pyridine ring. In practice, however, only one product (1) was isolated.

Clearly parvine may be synthesised by a similar sequence using nicotinoyl chloride (4, R=H), rather than (4, R=COMe) and omitting the last step. When harmalan (3) and nicotinoyl chloride were combined in dimethylformamide solution and the product worked up by extraction with aqueous acid the 2-acetylindole (6) was obtained rather than the required intermediate (5, R=H). Presumably this product arises from (5, R=H) by hydrolysis, for when aqueous conditions of isolation are avoided the amide (5, R=H) is obtained in fair yield. Oxidative cyclisation of (5, R=H) by irradiation with "soft" UV light then afforded a single compound identical in mp, mmp, IR spectroscopy with parvine.



To check that cyclisation of (5, R=H) had occurred via C_4 to give (2) the methiodide of the latter was prepared and its PMR spectrum in trifluoroacetic acid determined. The result demonstrates most clearly that the structure (2) for parvine is correct, for now the H atom attached to C_{17} resonates as a singlet at δ 9·5, and C_{20}-H and C_{21}-H form an AB system with doublets (J 6Hz) at δ 7·9 and 8·4 respectively.

The bark of *N. parva* also contains β-sitosterol, campesterol and stigmasterol as well as traces of a terpenoid acid, mp 293–5° (MeOH) (measured mass 588·400; calc. for $C_{35}H_{56}O_7$, 588·403 and for $C_{42}H_{52}O_2$, 588·397). Two other alkaloids $C_{20}H_{20}N_2O_3$ (measured mass 336·148; calc. mass 336·147) and $C_{20}H_{14}N_2O_2$ (measured mass 314·104; calc. 314·106) occur in very small amounts in the bark and the structures of these will be examined further when more plant material becomes available.

DISCUSSION

The occurrence of pyridino-indolo-quinolizidones in Rubiaceous plants and also in species from the Loganaciae is taxonomically interesting, although their ubiquity in the latter [2] has caused their authenticity as alkaloids to be questioned and there has been some discussion as to their origins either as natural products or as artefacts [1d,2,3].

In our work the use of nitrogenous reagents or basic conditions during the isolation procedure were avoided and chromatographic analysis indicated the presence of parvine at the very earliest stages of the work up, thus although this is not conclusive evidence, we tend to the view that parvine is a true alkaloid of *N. parva*.

EXPERIMENTAL

Isolation of parvine. Air dried bark (400 g) was pulverized and extracted (Soxhlet) with MeOH (10 l.). Removal of solvent afforded a brown gum (10 g) which was applied to a column of Si gel and eluted first with $CHCl_3$ petrol mixtures and then with $CHCl_3$–MeOH 60–80° in 175 10-ml fractions. Early fractions, on work up, yielded a mixture of campesterol, β-sitosterol and stigmasterol as well as traces of a terpenoid acid (see above). Fractions 62–71 (1–5% MeOH in $CHCl_3$) were combined and, after removal of the solvent, the residue was further purified by chromatography on 1 m plates coated with 2 mm thick layers of Si gel, eluting with Et_2O. The major band, R_f 0·5–0·6 was removed and extracted with MeOH to yield 0·3 mg of a highly fluorescent solid, mp 230–40° dec, molecular formula $C_{20}H_{14}N_2O_2$, λ_{max} 265, 295, 350, 372, 415 nm, ν_{max} 3360, 1690, 1630, 1600 cm^{-1} (nujol mull). Similarly fractions 72–89 (5–10% MeOH in $CHCl_3$) when combined and rechromatographed on plates, yielded, as the major component, a yellow gum (0·1 mg) $C_{20}H_{20}N_2O_3$, λ_{max} 316, 405 nm, ν_{max} 3240, 1740, 1650, 1600 cm^{-1}. Fractions 89–123 (10–15% MeOH in $CHCl_3$), on combination and removal of solvent, gave a brown gum (10 mg), this was separate by TLC on Si gel eluting with 5% MeOH in $CHCl_3$. The major band

R_f 0·55–0·61 was removed and extracted with MeOH to yield parvine as an orange coloured solid (4 mg) mp 292–4 (aq. MeOH) *m/e* 287 (100%), 286 (80%), 272 (15%): δ (TFA) 9·65 broad doublet [1H] (H-17); 8·45 *m*, [1H] (H-21); 8·05–7·20 *m* [6H] (aromatics) 4·78 *t*, *J* 7Hz, [2H] (H_2–6); 3·22 6 *J* 7Hz, [2H] (H_2–6), ν_{max} 3250, 1650, 1610 1600 cm^{-1}. [Found: C, 75·0; H, 4·4; $C_{18}H_{13}N_3O$ requires C, 75·2; H, 4·6%].

Synthesis of parvine. Reaction of harmalan with nicotinoyl chloride. Nicotinoyl chloride, generated *in situ* from its hydrochloride (0·8 g) salt by treatment with a 4-fold excess of triethylamine, was reacted with harmalan (1 g) in DMF soln. Solvent was removed under red. pres. and residue extracted with 2M HCl, basification of the extracts afforded the indole (6) mp 160–5° (EtOH), 0·6 g. *m/e* 307 (10%) 264 (5%), 185 (100%). δ (D_6-DMSO) 9·0 *bs* [2H], 8·8 *bs* [1H], 8·7 *bd* [1H], 8·2 *bd* [1H], 7·85–7·0 *m* [5H], 3·5 *m* [4H], 2·62 *s* [3H]. ν_{max} 3340, 1665, 1640 cm^{-1}. [Found: C, 70·5; H, 5·5; N, 13·5 $C_{18}H_{17}N_3O_2$ requires: C, 70·3; H, 5·6; N, 13·7%]. When this reaction was repeated, this time using CH_2Cl_2 as solvent instead of DMF and the residue, after evaporation of the solvent, applied to a column packed with Si gel and eluted with 2% MeOH in dry Et_2O the required product (**5**) was obtained. Yield 0·65 g, almost colourless plates, mp 101–5° (dec.) (softens at ~80°) *m/e* 289 (50%), 288 (25%), 261 (65%), 260 (100%), 106 (45%). ν_{max} 3300, 1645, 1610, 1590 cm^{-1}. δ ($CDCl_3$) 9·3 [1H] *s* (NH); 8·74 [2H] *bs*; 7·95–7·10 [6H]; 5·15 [1H] *m*; 4·3 [1H] *m*; 4·25 [2H] *t*, *J* 7Hz; 3·08 [2H] *t*, *J* 7Hz. [Found: C, 74·6; H, 5·0; N, 14·3 $C_{18}H_{15}N_3O$ requires: C, 74·7; H, 5·2; N, 14·5%]. This product (0·4 g) in MeOH (500 ml) was irradiated with "soft" UV light during 24 hr. Solvent was reduced in vol. to *ca* 50 ml and cooled; crystals of parvine formed around the edges of the flask, these were collected and recrystallized from MeOH. Yield 48%. mp 292–4°, mmp with natural parvine 293–4°. [Found: C, 75·2; H, 4·5; N, 14·3 Calc. for $C_{18}H_{13}N_3O$ C. 75·2; H, 4·6; N, 14·6%. Methiodide: yellow crystalline solid mp 330°. δ (TFA) 9·5 [1H] *s* (17-H); 8·3 [1H] *d*, *J* 6Hz (21-H); 7·9 [1H] *d*, *J* 6Hz (20-H); 7·68–7·2 [4H] *m* (9-H, 10-H, 11-H, 12-H); 7·20 [1H] *s* (14-H); 4·75 [2H] *t*, *J* 7Hz (5-H_2); 3·4 [2H] *t*, *J* 7Hz (6-H_2); 4·4 [3H] *s* (N-Me) [Found: C. 53·1; H, 3·8; N, 10·0 $C_{19}H_{16}N_3OI$ requires: C, 53·2; H, 3·75; N, 9·8%]. Parvine, at 50 mg/kg, showed no effect *in vivo* (mice); *in vitro* it produced non-specific contractions of the guinea pig ileum, and reduced the tone and activity of the rabbit duodenum preparation.

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POLYSTYRENE SPHERULES IN THE SEVERN ESTUARY

A PROGRESS REPORT

(Marine Pollution Bulletin, 1976, 7(3), 52)

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Polystyrene Spherules in the Severn Estuary – A Progress Report

In September 1973 we drew attention (Kartar *et al.*, 1973) to the presence of large amounts of polystyrene spherules of 1 mm diameter in the mud and sediment of the Severn Estuary and Bristol Channel and also to their ingestion by the fish population.

Since that time our investigations have continued and we now report that this form of pollution has virtually ceased, thus few spherules are to be found, at least in the upper layers of sediment, and the stomachs and intestines of four common fish species no longer contain them.

Significantly, our results given in Table 1, show that the intake of spherules into the flounder (*Platichthyes flesus*) at Oldbury on Severn reached a peak in the summer and autumn of 1973 but thereafter rapidly declined. The percentage of sea snails (*Liparis liparis*) found to contain polystyrene at Oldbury in 1974 was only 5% whereas at Hinkley, lower down the estuary, 25% of this species were heavily contaminated at this time.

The same trend is noted for five bearded rocklings (*Ciliata mustela*), but unfortunately we do not have comparable measurements at the two sites for flounders. It would appear, however, that this species is particularly prone to this type of contamination since the spherules were always more abundant in Bridgewater Bay than at Oldbury.

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Kartar, S., Milne, R. A. & Sainsbury, M. (1973). Polystyrene waste in the Severn Estuary, *Mar. Pollut. Bull.*, 4, 144.

TABLE 1
The occurence of polystyrene spherules as a percentage of the number of fish examined.

Locality	Date	Species	Total no. examined	Percentage fish containing polystyrene spherules
Oldbury	October 1972	Flounders (*Platichthyes flesus*)	54	5.5
	June 1973	Flounders (*Platichthyes flesus*)	530	20.7
	April–May 1974	Flounders (*Platichthyes flesus*)	100	10.1
	October–December 1974	Flounders (*Platichthyes flesus*)	206	5.0
	Jan–June 1975	Flounders (*Platichthyes flesus*)	200	nil
	1974	Sand goby (*Gobius minutus*)	50	5.0
	1975	Sand goby (*Gobius minutus*)	100	nil*
	1973/74	Sea snail (*Liparis liparis*)	50	6.5
	1974/75	Sea snail (*Liparis liparis*)	100	nil
	1974	Five Bearded Rockling	50	2.0
	1975	(*Ciliata mustela*)	5	nil
Hinkley	1974	Sand Goby	50	25.0
	1974	Sea Snail	50	25.0
	1975	Sea Snail	20	nil
	1974	Five Bearded Rocklings	50	10.0
	1975	Five Bearded Rocklings	8	nil

*Personal communication from C. Williams, Dept. of Zoology, University of Bath.

Intramolecular Coupling of Diaryl Amides by Anodic Oxidation

By **Malcolm Sainsbury** * and **John Wyatt**, School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY

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PERKIN TRANSACTIONS I

1976

Intramolecular Coupling of Diaryl Amides by Anodic Oxidation

By Malcolm Sainsbury * and John Wyatt, School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY

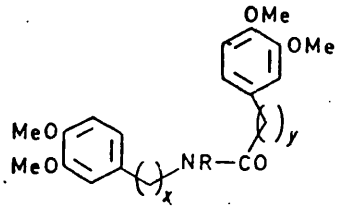
A series of diaryl amides have been converted by electrochemical oxidation into biphenyl derivatives. Limitations to this type of intramolecular coupling reaction, both steric and electronic, are discussed, and some novel dibenzazepine and dibenzazocine structures are described.

PHENOLIC oxidative coupling reactions are frequently key steps in the biosynthesis of natural products, particularly alkaloids.[1] Such reactions can often be replicated in the laboratory by using inorganic oxidants in alkaline media but, although this is an important synthetic route to several structures of pharmacological interest, yields in general are low and the work-up procedure is complicated by the necessity of handling polyhydric phenols in the presence of strong base.

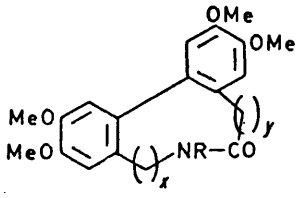
Other methods of aryl–aryl coupling, such as Pschorr or photochemical reactions, are also commonly employed in synthesis but each presents problems either in the inaccessibility of starting materials or in non-selectivity.

Hence there is a requirement for a more convenient technique of aryl–aryl coupling, and it has been claimed that for oxygenated ring systems this is provided by controlled anodic oxidation.[2] Thus electrochemical oxidation of aryl alkyl ethers at low anode potentials (*ca.* 1 V) generates radical cations which then undergo coupling and further oxidation to afford biphenyls. Previously, however, most examples illustrating this method have been directed at specific targets in which the aryl nuclei to be joined are favourably disposed to one another. Here we report a series of experiments designed to test steric requirements for intramolecular cyclization and also to study the effect of substituents.

First we considered amides of type (1) and their oxidative cyclisation to the biphenyl derivatives (2). Four



(1) R = H
(6) R = Me

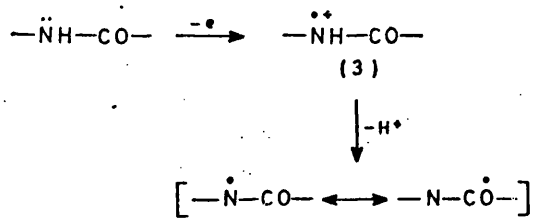


(2) R = H
(7) R = Me

amides were prepared (1; $x = y = 0$; $x = y = 1$; $x = 1$, $y = 2$; $x = 2$, $y = 1$); these were oxidized in acetonitrile solution, containing anhydrous sodium perchlorate as supporting electrolyte, at an anode potential [*vs.* standard calomel electrode (s.c.e.)] corresponding to the midpoint of the first oxidation wave as determined by a combination of polarographic curves (rotating platinum microanode and mercury cathode) and cyclic voltammetry.

We noted that $E_{\frac{1}{2}}$ for this wave is +1.0—1.2 V, which corresponds closely to that at which anisole and many other methoxylated aromatic compounds lose an electron to form the appropriate radical cation,[3] but during preparative electrolyses of each of the above amides at this anode potential an initial high current through the cell rapidly fell almost to zero and resinous material was deposited on the anode surface. Similar results were obtained with a variety of solvent, supporting electrolyte, and electrode systems: pulsing techniques were also unsuccessful.

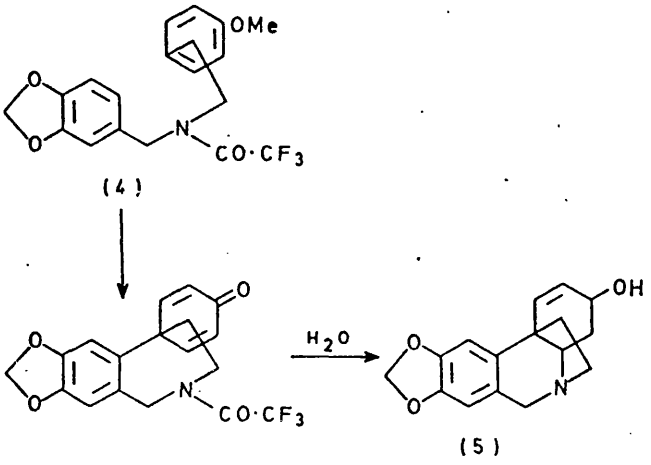
Here the common structural element is a secondary amide function and failure to cyclise, particularly in the cases $x = y = 1$, $x = 1$, $y = 2$, and $x = 2$, $y = 1$, is probably due to a combination of adverse conformational effects [4] and competing electro-oxidation processes at this site. Thus in the last case, for example, an initially formed cation radical (3) might undergo deprotonation to a radical which then subsequently yields resinous products (*N*-phenylbenzamide gives a poorly defined oxidation wave at an anode potential of *ca.* 1.2 V in acetonitrile–sodium perchlorate). Support of this view is



provided by the successful synthesis of (±)-oxocrinine (5)[5] *via* anodic oxidation of the tertiary amide (4); here radical formation by the above mechanism is impossible. Indeed, when the amides (6; $x = y = 1$) and (8) were prepared and oxidized at anode potentials of *ca* 1.1 V the tricyclic structures (7; $x = y = 1$) and (9) were obtained (45 and 60%, respectively). Structural assignments for these products follow from analytical and spectroscopic data (see Experimental section), but additionally, on

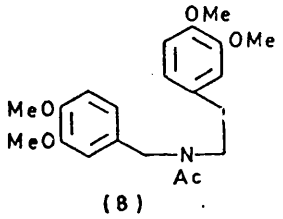
[1] Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Dekker, New York, 1967; T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.
[2] A. Ronlán and V. D. Parker, *Chem. Comm.*, 1970, 1567; see also S. Tobinaga, *Bio-organic Chem.*, 1975, **4**, 110, and references cited therein.
[3] M. Sainsbury, *J. Chem. Soc.* (*C*)., 1971, 2888.
[4] B. F. Pederson, *Acta Chem. Scand.*, 1967, **21**, 1422.
[5] E. Kotani, N. Takeuchi, and S. Tobinaga, *J.C.S. Chem. Comm.*, 1973, 550.

reduction with lithium aluminium hydride, the corresponding amines (10) and (11) were obtained, both of which were also fully characterized.

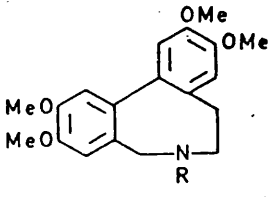


(4) (5)

Oxidation of compound (6; $x = 1, y = 0$) on the other hand gave a complex mixture of products from which only 2% of compound (7; $x = 1, y = 0$) was obtained. The related substrate (6; $x = y = 0$) gave only a resinous



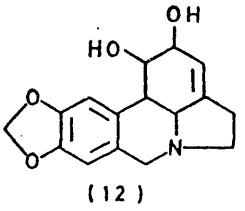
(8)



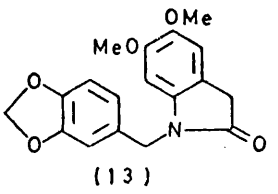
(9) R = Ac
(10) R = Me
(11) R = Et

product on electrolysis. In these two examples electronic interactions between one or both the aryl rings and the amide function are possible so it is reasonable to assume that the potentials at which the electrons of the individual rings are ionized are not the same, thus enhancing the possibilities of inter- rather than intramolecular coupling and hence the formation of mixtures. Thus Ronlán and his co-workers [6] have observed that where units of only slightly differing structures are present, both inter- and intra-molecular processes may occur. For example, 3,3',4-trimethoxybibenzyl yields a dimeric structure when oxidized at a low current density, whereas at higher current density both the dimer and an intramolecularly coupled product are formed, indicating that the dimethoxylated ring is more easily ionized to the corresponding radical cation than is its monomethoxylated counterpart.

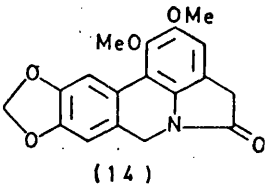
For some years we [7] have been interested in the synthesis of alkaloids of the lycorine (12) type, and it occurred to us that anodic oxidation of the oxindole derivative (13) followed by *ortho–para*-coupling might afford the lycorine model (14), although we recognized that the *para–para* product (15) was probably the more likely. The starting material was prepared by the route outlined in the Scheme, but despite encouraging preliminary analysis which revealed oxidation waves at anode potentials



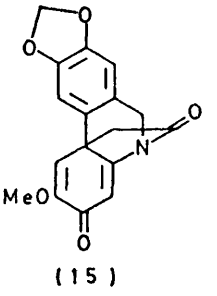
(12)



(13)

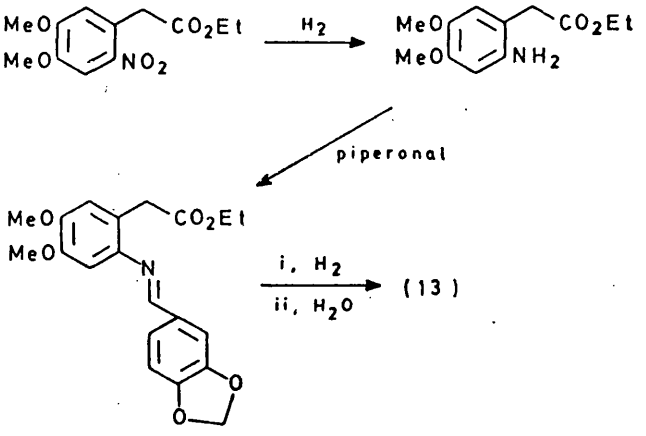


(14)



(15)

$E_{\frac{1}{2}}$ 0.8 and 1.1 V (*vs.* s.c.e.), a preparative electrolysis at the lower potential gave only a tar. This lack of specificity was a disappointment especially since we have already observed [8] that electrolysis of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (16) affords the spirocyclohexadienone (17) in excellent yield. The lactone (16) is however, not a good model for the present work and we next turned to the 3-benzyloxindole (18).



SCHEME

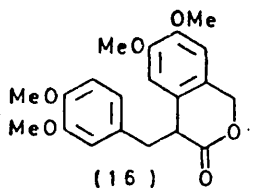
This, like (13), shows two anodic waves, $E_{\frac{1}{2}}$ 0.75 and 1.1 V (*vs.* s.c.e.), and similarly an oxidation attempt at the

[6] A. Ronlán, O. Hammerich, and V. D. Parker, *J. Amer. Chem. Soc.*, 1973, **95**, 7132.

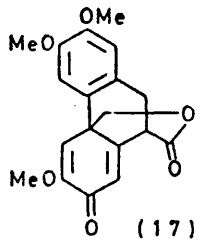
[7] S. F. Dyke, M. Sainsbury, and J. R. Evans, *Tetrahedron*, 1973, **29**, 213.

[8] M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1972, 718.

first value resulted only in an intractable gum. However at an anode potential of 1.1 V and a higher current density a 15% yield of the tetracyclic compound (19) was obtained, after work-up. A second electrolysis of (13),

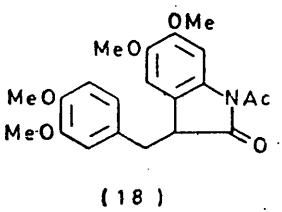


(16)

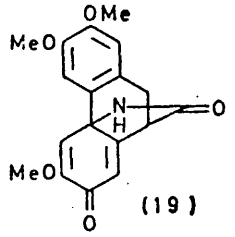


(17)

this time at 1.1 V and at high current density, however, also proved unrewarding and gave only a tar.



(18)



(19)

The dienones (15) and (19), which contain a five-membered ring, are more strained than the spirocyclohexadienone (17), and our results suggest that both inter- and intra-molecular processes may occur in the oxidation of their precursors, the former leading to complex products. The product (19) does not contain an acetyl function; although deacetylation may have occurred during electrolysis it seems more probable that the method of isolation, which involved chromatography over basic alumina, is responsible.

The above observations show that alkoxylated diaryl secondary amides are not suitable substrates for intramolecular coupling by anodic oxidation, but satisfactory results are obtained with their tertiary analogues especially when the aryl rings to be joined are uniformly substituted. We, in common with other workers,[9] have shown, however, that union *para–para* to alkoxy-groups is the preferred reaction course, so that although certain alkoxylated dibenzazocine, dibenzazepine, and possibly larger ring systems are available by this technique, the approach is limited and problems arise when multicyclic products have unfavourable stereochemistry, even though this may be a relatively minor constraint.

EXPERIMENTAL

All electrolyses were conducted with an H-type cell of 200 cm³ capacity, with dry acetonitrile as solvent and anhydrous sodium perchlorate as supporting electrolyte. The anode was a platinum gauze and the cathode a mercury pool. Current was provided by a Farnell stabilized power supply and the potential of the anode was monitored with a digital voltmeter *via* an agar bridge and a standard calomel electrode.

U.v. spectra were recorded for solutions in aqueous 95% ethanol; i.r. spectral data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at 100 MHz with tetramethylsilane as internal standard.

6-*Acetyl*-5,6,7,8-*tetrahydro*-2,3,10,11-*tetramethoxydibenz*[c,e]*azocine* (9).—*N*-Acetyl-*N*-veratryl-3,4-dimethoxyphenethylamine (8) (2 g) and anhydrous sodium carbonate (1 g) were added to the anode compartment of the cell which contained a 10% solution of sodium perchlorate in acetonitrile. The electrolysis was conducted at a controlled anode potential of 1.15 V until the equivalent of 1.9 F mol^{-1} of substrate had been utilized; then the contents of the anode compartment were separated and diluted with water (200 cm³). Most of the acetonitrile was removed by distillation and the solution was extracted several times with chloroform. Evaporation of the extracts afforded a gum which was chromatographed on neutral alumina (elution with chloroform–petroleum) to yield the *azocine* (1.2 g) as prisms, m.p. 190° (from ethanol–ether); $\lambda_{max.}$ 215, 259, and 283 nm; $\nu_{max.}$ 1 665sh, 1 630, and 1 600 cm^{-1}, δ ($CDCl_3$) 2.18 (3 H, s, Ac), 3.1 (1 H, d, J 14 Hz) and 5.3 (1 H, d, J 14 Hz) (5-H_2), 2.22—3.40 (4 H, m, 7- and 8-H_2) 3.95 (12 H, s, 4 × OMe), and 6.88 (1 H, s), 6.9 (1 H, s), 6.95 (1 H, s), and 7.6 (1 H s) (aromatic): *m/e* 343 (M^+) (Found: C, 67.9; H, 6.7; N, 3.7. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%).

6-*Ethyl*-5,6,7,8-*tetrahydro*-2,3,10,11-*tetramethoxydibenz*[c,e]*azocine* (11).—The product (9) (0.5 g) was dissolved in tetrahydrofuran (50 cm³) and an excess of lithium aluminium hydride was added. The mixture was then heated under reflux for 3 h, the excess of reagent was destroyed with ethyl acetate, water was added, and the mixture was extracted with chloroform. The extracts were evaporated to yield *compound* (11) as a gum which crystallized on trituration with ether; yield 0.4 g, m.p. 95—96°; $\lambda_{max.}$ 214, 258, and 283 nm; $\nu_{max.}$ 1 600 and 1 505 cm^{-1}; δ ($CDCl_3$) 1.1 (3 H, t J 6 Hz, Me), 2.2—4.0 (8 H, m 4 × CH_2), 3.8—4.0 (12 H, 2 × s, 4 × OMe), and 6.75—7.0 (4 × 1 H, s, aromatic) (Found: C, 70.5; H, 7.6; N, 3.9. $C_{21}H_{27}NO_4$ requires C, 70.6; H, 7.6; N, 3.9%).

5,8-*Dihydro*-2,3,10,11-*tetramethoxy*-6-*methyldibenz*[c,e]*azocin*-7(6H)-*one* (7; $x = y = 1$).—Conditions for the electrolysis of *N*-methyl-*N*-veratryl-3,4-dimethoxyphenylacetamide (6; $x = y = 1$) were as described for the analogue (8). Similar work-up procedures gave the *azocine* (7; $x = y = 1$) (45%), m.p. 204—205°; $\lambda_{max.}$ 218, 235sh, 265, and 283 nm; $\nu_{max.}$ 1 640, 1 605, and 1 510 cm^{-1}; δ ($CDCl_3$) 3.2 (3 H, s, NMe), *ca.* 3.9br (16 H, s, 5- and 8-H_2 and 4 × OMe), and 6.90—6.95 (4 × 1 H, s, aromatic) (Found: C, 66.0; H, 6.7; N, 3.9. $C_{19}H_{23}NO_5$ requires C, 66.1; H, 6.7; N, 4.1%).

5,6,7,8-*Tetrahydro*-2,3,10,11-*tetramethoxy*-6-*methyldibenz*[c,e]*azocine* (10). Reduction of the product (7; $x = y = 1$) with lithium aluminium hydride afforded the *azocine* (10) (80%), m.p. 136—138° (from ether); $\lambda_{max.}$ 214, 258, and 283 nm; $\nu_{max.}$ 1 600 and 1 505 cm^{-1}, δ ($CDCl_3$) 2.5 (3 H, s, NMe), 2.55 (2 H, t, J 8 Hz, 7-H_2), 3.08 (1 H, d, J 14 Hz) and 3.52 (1 H, d, J 14 Hz) (5-H_2), 3.20 (2 H, t, J 8 Hz, 8-H_2), 3.90 (12 H, s, 4 × OMe), and 6.7—6.86 (4 × 1 H, s, aromatic) (Found: C, 69.9; H, 7.2; N, 4.2. $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.3; N, 4.1%).

6,7-*Dihydro*-2,3,9,10-*tetramethoxy*-6-*methyldibenz*[c,e]*azepin*-5-*one* (7; $x = 1$, $y = 0$).—This *product*, obtained (2%) by electrolysis of *N*-methyl-*N*-veratryl-3,4-dimethoxybenzamide, had m.p. 220—221° (from ethanol); $\lambda_{max.}$ 218,

[9] V. D. Parker, U. Palmquist, and A. Ronlán, *Acta. Chem. Scand* (*B*), 1974, 28, 1241.

248, and 282 nm; $\nu_{max.}$ 1 618, 1 600, and 1 583 cm^{-1}, *m/e* 343 (M^+, 100%), 314 (60), 165 (20), and 150 (20) (Found: C, 66.5; H, 6.2; N, 4.2. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

Ethyl 2-Amino-4,5-dimethoxyphenylacetate.—This compound, prepared from ethyl 2-nitro-4,5-dimethoxyphenylacetate [10] by hydrogenation in methanol over 10% palladium–carbon at 100 lb in^{-2}, had m.p. 59°, $\lambda_{max.}$ 239 and 301 nm; $\nu_{max.}$ 3 400, 3 200, 1 710, and 1 610 cm^{-1}, *m/e* 239 (M^+), 207, and 193. [In our hands it is stable although Walker [10] states that on warming decomposition occurred and he was unable to isolate it.]

Ethyl 4,5-Dimethoxy-2-(3,4-methylenedioxybenzylideneamino)phenylacetate.—The preceding product (6 g) and piperonal (4.15 g) were heated in xylene solution (150 cm^3) in a Dean-Stark apparatus for 6 h. The solvent was removed and the residue was triturated with ether and crystallized from ethanol as prisms (8 g, 80%), m.p. 94—95°; $\lambda_{max.}$ 285 and 352 nm; $\nu_{max.}$ 1 730, 1 720, 1 680, 1 620, 1 600, and 1 580 cm^{-1}, δ ($CDCl_3$) 1.7 (3 H, t *J* 8 Hz), 3.82 (2 H, s), *ca.* 4.0 (12 H, m), 4.18 (2 H q, *J* 8 Hz), 6.7—7.7 (5 H, m), and 8.40 (1 H, s), *m/e* 387 (M^+), 372, and 314.

Ethyl 4,5-Dimethoxy-2-(3,4-methylenedioxybenzylamino)-phenylacetate.—The foregoing compound in ethanol was hydrogenated over Adams catalyst at 40 lb in^{-2} during 5 h to give the title compound as *prisms* (89%), m.p. 89—90° (from diethyl ether); $\lambda_{max.}$ 250, 284, and 302 nm; $\nu_{max.}$ 3 400, 1 725, 1 610, and 1 590 cm^{-1}, *m/e* 389 (M^+).

5,6-Dimethoxy-1-(3,4-methylenedioxybenzyl)indolin-2-one (13).—The foregoing amine (5 g) was passed, in chloroform solution, through a column packed with basic alumina (Merck). Removal of the solvent afforded the *oxindole* (13), in almost quantitative yield; it crystallized from ethanol as needles, m.p. 102—103°; $\lambda_{max.}$ 277 and 301 nm; $\nu_{max.}$ 1 705, 1 619, 1 601, and 1 584 cm^{-1}; δ ($CDCl_3$) 3.48 (2 H, s), 3.70 (3 H, s), 3.75 (9 H, m), 4.72 (2 H, s), 6.30 (1 H, s), 6.71 (1 H, s), and 6.74 (3 H, m), *m/e* 343 (M^+), 192, and 151 (Found: C, 66.4; H, 6.2; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

*4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one.**—6,7-Dimethoxyisochroman-3-one (15 g) [11] and veratraldehyde (11.3 g) were treated with pyrrolidine (6.9 g) in portions and the mixture was then heated at 100 °C under nitrogen. After cooling, the solid yellow product was collected, washed with 5% acetic acid in ethanol, and recrystallized from ethanol to give *needles* (19.3 g, 75%), m.p. 176—177°; $\lambda_{max.}$ 213 (ε 16 600), 250 (10 900), and 370 nm (12 100) (Found: C, 67.3; H, 5.7. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.7%).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (16).—The foregoing product (2.03 g) in glacial acetic acid (250 cm^3) was hydrogenated over Adams catalyst (0.3 g) at 60 lb in^{-2} until the solution became colourless (*ca.* 15 h). The catalyst and solvent were removed, and the residue crystallized from ethanol, as plates (1.96 g, 96.6%), m.p. 104—105°; $\lambda_{max.}$ 213 (ε 19 550) and 285 nm (6 340); $\nu_{max.}$ 1 750 cm^{-1}; δ ($CDCl_3$) 3.17 (2 H, d, *J* 8 Hz, 4-CH_2), 3.69, 3.75, and 3.84 (13 H, br, s, 4 × OMe and 4-H), 4.8 (2 H, q, *J* 14 Hz 1-H_2), and 6.42—6.8 (5 H, m, aromatic) (Found: C, 67.3; H, 6.3. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%).

Electrochemical Oxidation of Compound (16).—The isochroman-3-one was oxidized in the normal way at an anode potential of 1.22 V to give, after work-up, *9,10-dihydro-3,6,7-trimethoxy-4α,10-methanoxymethanophenanthrene-2,11-dione* (17) as needles, m.p. 256—257° (from ethanol); yield 70—80%; $\lambda_{max.}$ 265 (ε 6 650), 290 (4 180), and 360 (nm (4 750); δ ($CDCl_3$) 3.17br (3 H, s), 3.77 (3 H, s), 3.93 (6 H, s), 4.1 (2 H, q *J* 14 Hz), 5.98 (1 H, s), 6.53 (1 H, s), 6.78 (1 H, s), and 6.97 (1 H, s) (Found: C, 66.5; H, 5.4. $C_{19}H_{18}O_6$ requires C, 66.6; H, 5.3%).

Electrolysis of 1-Acetyl-5,6-dimethoxy-3-veratrylindolin-2-one (18).—*Compound* (18), m.p. 102—104° (Found: C, 65.4; H, 6.0; N, 3.6. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%), was prepared from 5,6-dimethoxy-3-veratrylideneindolin-2-one [16] by hydrogenation and treatment of the product with acetic anhydride, and was electrolysed at an anode potential of 1.10 V. A high current density was employed and it became necessary to cool the cell with an ice–water bath. *9,10-Dihydro-3,6,7-trimethoxy-4α,10-iminomethanophenanthrene-2,11-dione* (19) was obtained after chromatography; yield 15%, m.p. 286—288° (from ethanol); $\nu_{max.}$ 3 310, 1 740, 1 650, 1 635, and 1 610 cm^{-1}; δ [10% $(CD_3)_2SO$ in $CDCl_3$] 3.40br (3 H, s, CH_2·CH), 3.65, 3.8, and 3.9 (each H, s, (OMe), and 5.8, 5.95, 6.50, and 6.87 (each 1 H, s, olefinic or aromatic); *m/e* 327 (M^+) (Found: C, 65.9; H, 5.1; N, 4.4. $C_{18}H_{17}NO_5$ requires C, 66.0; H, 5.2; N, 4.3%).

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* We thank R. F. Schinazi for conducting these experiments (see ref. 8).

[10] G. N. Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 3844.
[11] T. S. Stevens, *J. Chem. Soc.*, 1927, 178; J. Finkelstein, U.S.P. 3,480,634 (*Chem. Abs.*, 1970, **72**, 43,486s).

CHEMISTRY OF 6H-PYRIDO[4,3-b]CARBAZOLES PART V: A SIMPLE SYNTHESIS OF ELLIPTICINES

(J.Chem.Soc.Perkin 1, 1976, 1155)

Chemistry of 6*H*-Pyrido[4,3-*b*]carbazoles. Part V.[1] A Simple Synthesis of Ellipticines

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A new versatile synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) is described which requires mild conditions and utilises easily accessible starting materials [indoles and 3-(1-chloroalkyl)pyridines]. It is illustrated by the synthesis of 11-demethylellipticine, ellipticine, and 8,9-methylenedioxyellipticine. Overall yields compare favourably with those of previous syntheses.

SINCE certain 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) show promise as potential anticancer drugs,[2] numerous synthetic routes to them have been devised.[1a,3] There are, however, problems inherent in all preparations so far described, and our intention has been to develop an efficient synthesis of wide application requiring both readily available starting materials and the mildest reaction conditions. In view of this we have always been attracted by the simplicity of Woodward's original three-step sequence to ellipticine (2; R = Me)[4a] (Scheme 1). Unfortunately this route has no practical

[1] (*a*) Part IV, M. Sainsbury, B. Webb, and R. F. Schinazi, *J.C.S. Perkin I*, 1975, 289; (*b*) preliminary report M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1975, 540.

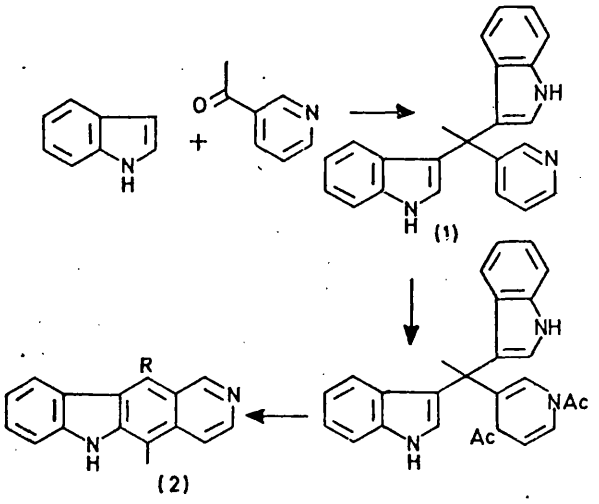
[2] M. Hayat, G. Mathé, M. M. Janot, P. Potier, N. Dat-Xuong, A. Cavé, T. Sévenet, C. Kan-Fan, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, 1974, **21**, 101, and references cited therein.

[3] (*a*) P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3842; (*b*) T. R. Govindachari, S. Rajappa, and V. Sundarsanam, *Indian J. Chem.*, 1963, **1**, 247; (*c*) L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Austral. J. Chem.*, 1967, **20**, 2715; (*d*) F Le Goffic, A. Gouyette, and A. Ahond, *Compt. rend.*, 1972, **274C**, 2008; (*e*) T. Kametani, Y. Ichikawa, T. Suzuki, and F. Fukumoto, *Tetrahedron*, 1974, **30**, 3713; (*f*) R. Besselievre, C. Thal, H. P. Husson, and P. Potier, *J.C.S. Chem. Comm.*, 1975, 90; (*g*) K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264; (*h*) M. Sainsbury and B. Webb, *ibid.*, 1974, 1560; (*i*) R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, and R. W. Kierstead, *J. Medicin. Chem.*, 1975, **18**, 755; (*j*) Y. Langlois, N. Langlois, and P. Potier, *Tetrahedron Letters*, 1975, 955.

[4] (*a*) R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Amer. Chem. Soc.*, 1959, **81**, 4434; (*b*) J. Bergman and R. Carlsson, *J. Heterocyclic Chem.*, 1972, **9**, 833.

value since the overall yield is extremely low and the conditions in the final step are severe. These disadvantages arise because the second stage operates through a complex dimerisation–disproportionation mechanism [5] for which the bulky intermediate (1) is a poor substrate and, in the final oxidative cyclisation reaction, the 'extra' indolyl unit is only removed with difficulty, under pyrolytic conditions.

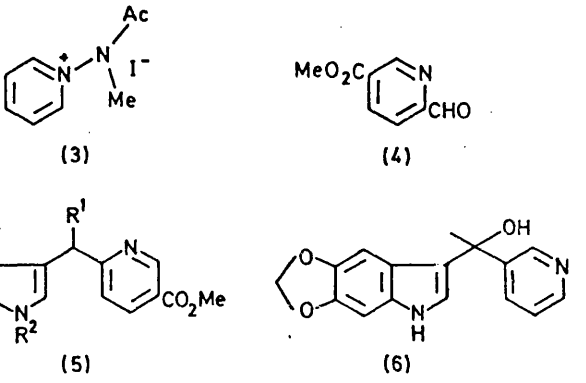
We considered that if the conditions for the initial condensation between the indole and pyridine units could be moderated to afford a '1 : 1' product, then these constraints would be partly removed although, necessarily, the second stage (reductive acetylation) is limited to a maximum yield of 50%.[5] (In practice, even with simple pyridines, the yield is more usually 10—20%.[3g,h]) Suzue *et al.*,[6] however, have reported that pyridine can be converted into the *N*-amidopyridinium salt (3), which with potassium cyanide gives 4-cyanopyridine. This reaction has wide application



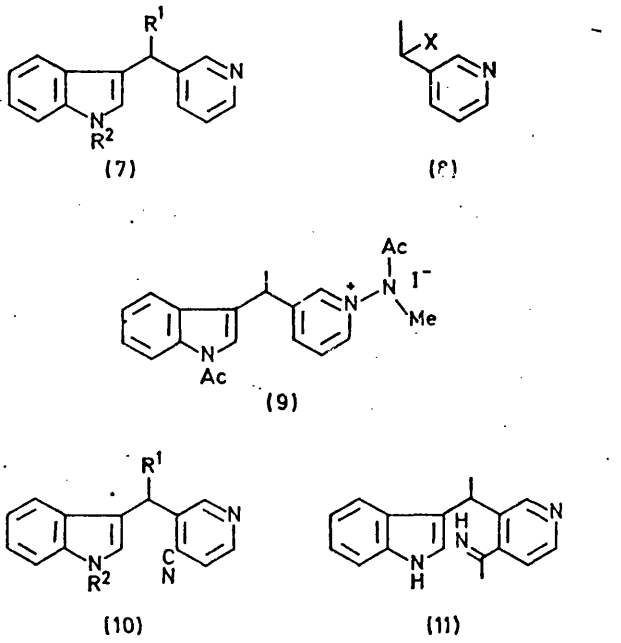
SCHEME 1

and from the product nitriles the corresponding acetyl derivatives are readily prepared by the action of methyllithium, followed by hydrolysis of the intermediate imine.[1a] Since the yields in this procedure are almost quantitative, we considered that the second obstacle to the Woodward approach was overcome, leaving only the problems of the condensation reaction to be solved.

Although acidic conditions favour a product containing two indolyl units,[4g,h] Potier has shown [7] that at room temperature the aldehyde (4) combines with indole in the presence of aqueous base to give the alcohol (5; $R^1 = OH$, $R^2 = H$); this on hydrogenolysis affords the 3-methylindole derivative (5; $R^1 = R^2 = H$). Unfortunately, 3-acetylpyridine is much less reactive than the aldehyde (4) towards indole: under Potier's conditions it does not react, and even with 5,6-methylenedioxyindole the reaction is very slow. Thus only a 2% yield of the alcohol (6) was obtained after 1 month. All attempts to accelerate these processes result in complex products.



It is known that 3-(halogenomethyl)pyridines and indolylmagnesium bromide give the corresponding 3-(pyridylmethyl)indole (7; $R^1 = R^2 = H$),[8] but at first we were prevented from repeating this reaction with the bromo-compound (8; X = Br) because treatment of the alcohol (8; X = OH) with phosphorus tribromide gave only polymeric products. However, when the alcohol was treated with toluene-*p*-sulphonyl chloride in the presence of sodium acetate, the acetate ester (8; X = OAc) was formed and, similarly, with methanesulphonyl chloride the chloro-compound (8; X = Cl) was obtained. (This last compound is stable at 0—10 °C.) Accordingly, a mixture of alcohol and indole in dry benzene was treated with methanesulphonyl chloride in the expect-



ation of forming compound (7; $R^1 = Me$, $R^2 = H$), and on work-up, a 30% yield of the required 3-ethylindole

[5] J. W. Wibaut and J. F. Arens, *Rec. Trav. chim.*, 1941, **60**, 119; P. M. Atlani and J. F. Bielmann, *Tetrahedron Letters*, 1969, 4829; P. M. Atlani, J. F. Bielmann, R. Briere, H. Lemaire, and A. Rassat, *Tetrahedron*, 1972, 2827.

[6] S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, 1973, **93**, 1331.

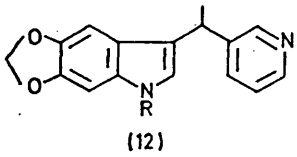
[7] Y. Langlois and P. Potier, *Tetrahedron*, 1975, **31**, 419.

[8] J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocyclic Chem.*, 1966, **3**, 67.

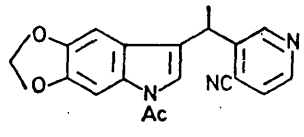
was obtained. The same product was also produced, in better yield (49.5%), by the action of indolylmagnesium bromide on the chloro-compound (8; X = Cl), prepared either as above or by treating the alcohol (8; X = OH) with thionyl chloride.

With the 3-ethylindole (7; R^1 = Me, R^2 = H) to hand, the remaining steps to ellipticine were easily accomplished in 25—30% overall yield. Thus the salt (9), prepared from the *N*-acetyl derivative (7; R^1 = Me, R^2 = Ac) by the action in turn of *O*-mesitylsulphonylhydroxylamine, acetic anhydride, and methyl iodide,[9] was treated with potassium cyanide and ammonium chloride to give the nitrile (10; R^1 = Me, R^2 = Ac). This was deacetylated by elution through a short column of basic alumina with chloroform as solvent; the product reacted with methyl-lithium and the intermediate imine (11) was hydrolysed and cyclised directly to ellipticine by warming in aqueous 20% acetic acid.

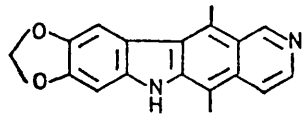
By the same procedures 11-demethylellipticine (2; R = H) was obtained from the 3-methylindole derivative (7; R^1 = R^2 = H) * (yield 28%), and 8,9-methylenedioxyellipticine (14) from (12; R = H) *via* the cyano-derivative (13) (overall yield 65%).



(12)



(13)



(14)

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol; i.r. data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at 60 or 100 MHz for solutions in deuteriochloroform unless stated otherwise, with tetramethylsilane as an internal standard.

Condensation Attempts between 3-Acetylpyridine and Indoles.—(*a*) Indole (1.16 g) and 3-acetylpyridine (1.21 g) in glacial acetic acid were heated under reflux for 2 h. After cooling, the mixture was poured into aqueous sodium hydroxide (7%; 8 cm^3). The solid formed was recrystallised from ethanol to give white prisms of 1,1-di-indol-3-yl-1-(3-pyridyl)ethane (1) (1.1 g, 33%), m.p. 251—252° (from ethanol) [lit.,[4b] 253° (decomp.)]; *m/e* 337 (M^+) and 322 (base).

(*b*) 5,6-Methylenedioxyindole [10] (1.61 g) in methanol (7.5 cm^3) and 10M-sodium hydroxide (0.14 cm^3) was cooled to 0 °C. To the stirred solution 3-acetylpyridine (1.21 g) was added dropwise at 0 °C, and the mixture was then stirred overnight at 0 °C. T.l.c. showed the presence of three components. The mixture was stored for 1 month at room temperature, during which time some crystals were formed. These were filtered off and washed with cold methanol to yield white prisms of 1-(5,6-*methylenedioxyindol*-3-*yl*)-1-(3-*pyridyl*)*ethanol* (6) (50 mg, 2%), m.p. 185—186° (from methanol), *m/e* 282 (M^+), 264 (base), 253, 239, and 255; $\nu_{max.}$ 3 540, 3 100, and 1 300 cm^{-1}; δ [$CDCl_3$–5% $(CD_3)_2SO$] 10.15br (1 H, s, NH), 8.7 (1 H, d, *J* 2 Hz, pyridyl 2-H), 8.4 (1 H, d, *J* 5 Hz, pyridyl 6-H), 7.8 (1 H, dd, *J* 5 and 2 Hz, pyridyl 4-H), 7.25 (2 H, m, indole 2- and pyridyl 5-H), 6.85 (1 H, s, indole 7-H), 6.8 (1 H, s, indole 4-H), 5.85 (2 H, s, O·CH_2·O), 5.13br (1 H, s, OH), and 1.94 (3 H, s, CH_3) (Found: C, 67.9; H, 5.1; N, 9.8. $C_{16}H_{14}N_2O_2$ requires C, 68.1; H, 5.0; N, 9.9%).

Nicotinoyl Chloride (*Optimised Procedure*).—Nicotinic acid (48 g) was heated at reflux for 30 min with thionyl chloride (150 cm^3) under anhydrous conditions. The excess of thionyl chloride was then removed by evaporation *in vacuo* and by azeotropic distillation with dry benzene. The white needles of nicotinoyl chloride hydrochloride were covered with ether and the mixture was stirred with dry triethylamine (40 g) overnight. The triethylamine hydrochloride formed was filtered off and the solution of nicotinoyl chloride in ether was stored under anhydrous conditions.

Indol-3-yl 3-Pyridyl Ketone.—The ethereal solution of nicotinoyl chloride was placed in an ice–salt bath, and a solution of indol-3-ylmagnesium bromide (1 mol equiv.) was added dropwise, with the temperature maintained between −5 and 0 °C. The mixture was stirred for a further 2 h at 0 °C and then left overnight at room temperature. The organometallic complex was hydrolysed with a saturated solution of ammonium chloride and the mixture was extracted several times with dichloromethane. The red organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to yield a thick gum. This was dissolved in propan-2-ol (200 cm^3) and cooled to furnish 3-*indolyl* 3-*pyridyl ketone* (21.4 g, 25%) as white cubes, m.p. 210—211°; $\lambda_{max.}$ 260sh (ε 14 350), 269 (14 750), and 322 nm (13 800); $\nu_{max.}$ 1 597 (C=O) and 3 175 cm^{-1} (N–H); δ [$(CD_3)_2SO$] 12.20br (1 H, s, NH), 9.05 (1 H, d, *J* 1.5 Hz, pyridyl 2-H), 8.80 (1 H, d, *J* 1.5 Hz, pyridyl 6-H), 8.0—8.50 (3 H, m, pyridyl 4- and 5- and indolyl 4-H), 7.2—7.70 (4 H, m, indolyl 2-, 5-, 6-, and 7-H), *m/e* 222 (M^+) and 144 (base) (Found: C, 75.5; H, 4.55; N, 12.45. $C_{14}H_{10}N_2O$ requires C, 75.65; H, 4.55; N, 12.45%).

N-*Acetylindol-3-yl 3-Pyridyl Ketone.*—3-Indolyl 3-pyridyl ketone (1.5 g) was heated under reflux for 1 h with acetic anhydride (30 cm^3). The solvent was removed by evaporation *in vacuo* and the residue crystallised from ethanol to furnish the title compound as pale yellow *needles* (86%), m.p. 173—175°; $\lambda_{max.}$ 210 (ε 19 600), 228 (26 500), 252 (14 400), and 309 nm (11 100); $\nu_{max.}$ 1 730 (NAc) and 1 630 cm^{-1} (vinylogous amide C=O); δ 9.04 (1 H, s, pyridyl 2-H), 8.78br (1 H, d, *J* 4.5 Hz, pyridyl 6-H), 8.0—8.47 (3 H, complex, pyridyl 4- and 5- and indolyl 4-H), 7.84 (1 H, s, indolyl 2-H), 7.24—7.51 (3 H, complex, indolyl 5-, 6-, and 7-H), and 2.62 (3 H, s, NAc) (Found: C, 72.5; H, 4.5; N, 10.7. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%).

Reduction of 3-Indolyl 3-Pyridyl Ketone with Sodium Borohydride.—(a) *Reduction at* 25 °C. The ketone (10 g) was dissolved in warm aqueous ethanol (300 cm^3) and

* Prepared by the action of nicotinoyl chloride on indolylmagnesium bromide and reduction of the product with sodium borohydride.

[9] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, **40**, 4133.

[10] F. Dallacker and D. Bernabei, *Monatsh. Chem.*, 1967, **98**, 785.

sodium borohydride was added in portions with stirring, with the temperature maintained at 25—30 °C. Addition of borohydride was stopped when the u.v. spectrum of the solution showed no further change. The excess of reagent was then decomposed by careful addition of acetone. The mixture was evaporated to dryness *in vacuo* at 45—50 °C and the residue partitioned between water (100 cm^3) and chloroform (100 cm^3). The organic phase was dried ($MgSO_4$) and evaporated to low bulk; *indol-3-yl-(3-pyridyl)-methanol* crystallised as needles (9.3 g, 92%), m.p. 154—155°, $\lambda_{max.}$ 268 (ε 8 000), 280sh (7 200), and 288 nm (6 140); $\nu_{max.}$ 3 270 (O–H), 3 140 (N–H), and 1 240 cm^{-1} (C–O); δ [$(CD_3)_2SO$] 10.55br (1 H, s, NH), 8.70br (1 H, s, pyridyl 2-H), 8.40br (1 H, d, *J* 5 Hz, pyridyl 6-H), 6.85—7.95 (7 H, m, remaining aromatic protons), 6.10 (1 H, d, *J* 4 Hz, C*H*·OH), 5.65 (1 H, d, *J* 4 Hz, OH) (on treatment with deuterium oxide the peak at δ 5.65 disappears and the signal at 6.10 collapses to a sharp singlet); *m/e* 224 (M^+) and 206 (base) (Found: C, 75.3; H, 5.4; N, 12.4. $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.4; N, 12.5%).

(b) *Reduction in boiling aqueous ethanol.* The ketone (1.5 g) was dissolved in 95% ethanol (50 cm^3) and an excess of sodium borohydride was added in portions to the boiling solution. After 30 min the solvent was removed *in vacuo* and the residue extracted with water and chloroform. The chloroform extract was washed, dried ($MgSO_4$), and evaporated to dryness. Trituration of the yellow gum with ether furnished a pale yellow amorphous solid (7; $R^1 = R^2 = H$) (1.0 g, 72%), which crystallised from acetone–ether as almost colourless cubes, m.p. 157—158° (lit.,[8] 154—156°), $\lambda_{max.}$ 270 (ε 8 500), 282 (7 400), and 291 nm (6 400); $\nu_{max.}$ 3 110 cm^{-1} (NH); δ 10.40br (1 H, s, NH), 8.50br (1 H, s, pyridyl 2-H), 8.35 (1 H, d, *J* 5 Hz, pyridyl 6-H), 6.9—7.8 (7 H, complex, remaining aromatic protons), and 4.05 (2 H, s, ArCH_2Ar); *m/e* 208 (M^+) and 92 (base) (Found: C, 80.3; H, 5.6; N, 13.5. Calc. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5%).

1-(3-*Pyridyl*)*ethyl Acetate* (8; X = OAc).—1-(3-Pyridyl)-ethanol (2 g) and toluene-*p*-sulphonyl chloride (5 g) were dissolved in benzene (60 cm^3) and solid anhydrous sodium acetate (1.3 g) was added. The mixture was heated and stirred on a steam-bath for 2 h, and then left at room temperature overnight. Water (50 cm^3) was added and the two phases were separated. The aqueous phase was basified with ammonia solution (*d* 0.89) and extracted with chloroform. The extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield the *acetate* as a yellow oil (0.5 g), b.p. 62° at 0.08 mmHg, $\nu_{max.}$ 1 730 and 1 235 cm^{-1}; $\lambda_{max.}$ 256, 262, and 270 nm; δ 8.7—5 (2 H, m, pyridyl 2- and 6-H), 7.8—7.55 (1 H, m, pyridyl 4-H), 7.35—7.10 (1 H, m, pyridyl 5-H), 5.9 (1 H, q, *J* 6.5 Hz, C*H*·CH_3), 2.05 (3 H, s, OAc), and 1.55 (3 H, d, *J* 6.5 Hz, CH·C*H*$_3$) (Found: C, 65.35; H, 6.6. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.7%). The same product was obtained from the alcohol by the action of acetyl chloride.

3-(1-*Chloroethyl*)*pyridine* (8; X = Cl).—The alcohol (8; X = OH) (2 g) in benzene was heated on a water-bath with methanesulphonyl chloride (1 cm^3) for 30 min. After cooling, water (50 cm^3) was added and the aqueous phase separated, basified, and worked up to give the title compound (0.8 g) as a mobile, unstable liquid, $\nu_{max.}$ 650 cm^{-1}. This compound has been prepared previously in this laboratory by the action of thionyl chloride on the alcohol (8; X = OH) and characterised by conversion into 3-(1-methoxyethyl)pyridine with sodium methoxide.[3g]

3-[1-(3-*Pyridyl*)*ethyl*]*indole* * (7; R^1 = Me, R^2 = H).—(*a*) Methanesulphonyl chloride (1 cm^3) in dry benzene was added slowly (4 h) to a mixture of indole (1.2 g) and the alcohol (8; X = OH) (1.2 g) in the same solvent under reflux in a Dean–Stark apparatus. At the end of the reaction the benzene was decanted from oil which had separated and the latter was then dissolved in water and washed several times with ether. The aqueous phase was basified with ammonia and extracted with chloroform; the combined chloroform extracts were dried and evaporated to give an orange-coloured oil. On trituration with benzene this gave the title compound as a colourless *solid* (0.7 g, 30%), m.p. 173—174°; *m/e* 222 (M^+), 207 (base), and 144; $\nu_{max.}$ 3 140, 1 590, 1 580, and 1 030 cm^{-1}; δ 8.7br (1 H, s, NH), 8.64 (1 H, d, *J* 2 Hz, pyridyl 2-H), 8.42 (1 H, dd, *J* 6 and 2 Hz, pyridyl 6-H), 7.6—6.9 (7 H, m, indole 2-, 4-, 5-, 6-, and 7- and pyridyl 4- and 5-H), 4.4 (1 H, q, *J* 10 Hz, C*H*·CH_3), and 1.7 (3 H, d, *J* 10 Hz, CH·C*H*$_3$) (Found: C, 81.0; H, 6.4; N, 12.4. $C_{15}H_{14}N_2$ requires C, 81.1; H, 6.4; N, 12.6%).

(*b*) An ethereal solution of ethylmagnesium bromide [from ethyl bromide (10.8 cm^3)] was placed in an ice–salt bath, and indole (16.56 g, 0.142 mol) in dry ether (35 cm^3) was added dropwise. After 30 min the indolylmagnesium bromide had settled as a dense grey suspension, leaving a colourless ether layer above. The suspension was allowed to warm to room temperature and then stirred for 1 h. The solution was then cooled to 0 to −5 °C and 3-(1-chloroethyl)pyridine (8; X = Cl) (8.86 g, 0.07 mol) was added rapidly. The solution was stirred for 1 h at 0 °C and then allowed to warm slowly to room temperature. The resulting mixture was stirred for 48 h at room temperature and then cooled to 0 °C. Hydrochloric acid (2M; 50 cm^3) was added and the mixture was shaken until most of the gum had dissolved. The layers were separated, and the aqueous layer washed with ether (50 cm^3), adjusted to pH 9—10 with concentrated ammonia, and extracted with chloroform (2 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil. On trituration with ether the oil afforded the title compound as a white solid which was filtered off and recrystallised from ethanol to yield prisms (7.7 g, 49.5%).

When a mixture of ethylmagnesium bromide, indole, and the chloropyridine (molar ratios 1 : 1 : 1) was used, a 22.4% yield of (7; R^1 = Me, R^2 = H) was obtained. Addition of benzene, tetrahydrofuran, or dichloromethane to solubilise the intermediate complex did not increase the yield of product. Heating the mixture of indolylmagnesium bromide and the chloropyridine (8; X = Cl) with or without the above-mentioned solvents, at any stage during the reaction, reduced the yield of final product.

1-*Acetyl*-3-[1-(3-*pyridyl*)*ethyl*]*indole* (7; R^1 = Me, R^2 = Ac).—Compound (7; R^1 = Me, R^2 = H) (3.43 g) was heated under reflux in acetic anhydride (20 cm^3) and triethylamine (4 cm^3) for 30 min. The solvent was removed *in vacuo*, and the oil obtained was dissolved in chloroform and basified with saturated aqueous sodium hydrogen carbonate. The organic layer was separated, dried ($MgSO_4$), and evaporated, to yield a solid which crystallised from ethanol as almost colourless *prisms* (3.9 g, 96%), m.p. 123—124°, *m/e* 264 (M^+), 222, 207 (base), and 144; $\nu_{max.}$ 1 685 and 1 600 cm^{-1}; δ 8.6 (1 H, d, *J* 1 Hz, pyridyl 2-H), 8.45 (1 H, d, *J* 7 Hz, pyridyl 6-H), 8.35 (1 H, s, indole 2-H), 7.48 (1 H, d, *J* 10 Hz, indole 7-H), 7.3—7.0

* We thank Mr. I. T. W. Matthews for this experiment.

(5 H, m, indole 4-, 5-, and 6- and pyridyl 4- and 5-H), 4.3 (1 H, q, *J* 7 Hz, C*H*·CH_3), 2.6 (3 H, s, Ac), and 1.7 (3 H, d, *J* 7 Hz, CH·C*H*$_3$) (Found: C, 77.1; H, 6.1; N, 10.7. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%).

3-[1-(*Indol-3-yl*)*ethyl*]*pyridine-4-carbonitrile* (10; R^1 = Me, R^2 = H).—1-Acetyl-3-[1-(3-pyridyl)ethyl]indole (7; R^1 = Me, R^2 = Ac) (2.59 g) was dissolved in dichloromethane (15 cm^3) and cooled to 0 °C. To this solution, *O*-mesitylsulphonylhydroxylamine (1 mol. equiv., 2.11 g) in cooled dichloromethane (20 cm^3) was added and the mixture was swirled. After *ca.* 15 min (with intermittent swirling) the solution was diluted with cooled, dry ether (250 cm^3), which caused an oil to separate. The ether was decanted, the oil was dissolved in ice-cooled water (25 cm^3), and acetic anhydride (20 cm^3) was added. The agitated mixture was then treated dropwise with aqueous 30% potassium hydroxide (15 cm^3) and maintained at room temperature for 1 h, before being poured into water (800 cm^3), basified with potassium carbonate, and extracted with chloroform. The organic phase was separated, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil, *m/e* 321 (M^+), 279, 264, and 222 (base).

This product was treated with methyl iodide (20 cm^3) at reflux during 45 min. Removal of the excess of reagent left a yellow amorphous solid (4.2 g, 77.8%). This salt (4 g) in water (15 cm^3) was warmed to 20—22 °C and treated with ammonium chloride (2 mol. equiv., 0.93 g) and potassium cyanide (0.62 g) in water (6 cm^3). This mixture was stored for 1 h, during which time a pink precipitate was formed. The mixture was extracted with chloroform to yield, after removal of the solvent, an oil which was stirred in ethanol solution and irradiated with 'soft' u.v. light for 30 min. The solvent was removed under reduced pressure and the viscous oily residue was dissolved in chloroform and chromatographed over a short column of basic alumina (chloroform as eluant).

The first fractions were evaporated to give the *nitrile* (10; R^1 = Me, R^2 = H) as white prisms (2.0 g, 95%), m.p. 118—119° (from ethanol); *m/e* 247 (M^+) and 232 (base); $\nu_{max.}$ 3 140, 2 240, and 1 580 cm^{-1}; δ 8.66 (1 H, d, *J* 2 Hz, pyridine 2-H), 8.55 (1 H, d, *J* 6 Hz, pyridine 6-H), 8.25br (1 H, s, NH), 7.5—6.9 (6 H, m, indolyl 2-, 4-, 5-, 6-, and 7- and pyridine 5-H), 4.76 (1 H, q, *J* 9 Hz, CH·CH_3), and 1.79 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 77.8; H, 5.2; N, 16.9. $C_{16}H_{13}N_3$ requires C, 77.7; H, 5.3; N, 17.0%).

When, however, the reaction was repeated but the product was chromatographed on neutral alumina, the *N-acetyl derivative* (10; R^1 = Me, R^2 = Ac) was obtained as white prisms, m.p. 111—112° (from ethanol); *m/e* 289 (M^+) 247 and 232 (base); $\nu_{max.}$ 2 240, 1 705, and 1 600 cm^{-1}; δ ($CDCl_3$) 8.67 (1 H, d, *J* 2 Hz, pyridine 2-H), 8.6 (1 H, s, indolyl 2-H), 8.44 (1 H, d, *J* 10 Hz, pyridine 6-H), 7.46—7.1 (5 H, m, indolyl 4-, 5-, 6-, and 7- and pyridine 5-H), 4.68 (1 H, q, *J* 8 Hz, C*H*·CH_3), 2.68 (3 H, s, Ac), and 1.85 (3 H, d, *J* 8 Hz, CH·C*H*$_3$) (Found: C, 74.8; H, 5.4; N, 14.6. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%).

Ellipticine (2; R = Me).—The nitrile (10; R^1 = Me, R^2 = H) (200 mg) in dry ether (25 cm^3) was added slowly to a solution of methyl-lithium (4 mol. equiv.) in ether at −10 to −15 °C under nitrogen. Stirring was continued for 30 min at the same temperature, and then ice-cold water (10 cm^3) was introduced, followed by ammonium chloride (200 mg) in water (10 cm^3). The ethereal layer was removed, dried, and evaporated *in vacuo* to give the imine (12) as a gum, *m/e* 263 (M^+), 248 (base), and 231; $\nu_{max.}$ 3 360, 3 200, 1 640, and 1 595 cm^{-1}. The gum was dissolved in acetic acid (20%; 10 cm^3) and heated on a steam-bath for 10 min. A yellow fluorescence immediately developed. The solution was basified with potassium carbonate and extracted with chloroform. The organic layer was dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow solid (188 mg, 92%), m.p. 311—312° (from chloroform) (lit.,[3g] 309—313°) (Found: C, 83.0; H, 5.6; N, 11.2. Calc. for $C_{17}H_{14}N_2$: C, 82.9; H, 5.7; N, 11.4%), identical (i.r. and u.v. spectra and chromatographic behaviour) with authentic ellipticine.[11]

11-*Demethylellipticine* (2; R = H).—The methylindole (7; R^1 = R^2 = H) was converted into its *N*-acetyl derivative (7; R^1 = H, R^2 = Ac) ($\nu_{max.}$ 1 720, 1 495, 1 460, and 1 050 cm^{-1}) which, without purification, was treated as described for (7; R^1 = Me, R^2 = Ac) to give, eventually, 3-[1-(1-*acetylindol-3-yl*)*ethyl*]*pyridine-4-carbonitrile* (10; R^1 = H, R^2 = Ac),* m.p. 157—158° (from ethanol); $\nu_{max.}$ 2 260 and 1 720 cm^{-1}; δ 8.84 (1 H, s, pyridine 2-H), 8.8—8.46 (2 H, m, pyridine 6- and indolyl 7-H), 7.64—7.28 (5 H, m, remaining aromatic protons), 4.32 (2 H, s, CH_2), and 2.64 (3 H, s, Ac) (Found: C, 74.2; H, 4.7; N, 15.2. $C_{17}H_{13}N_3O$ requires C, 14.1; H, 4.8; N, 15.3%). This compound was eluted in chloroform through a short column packed with basic (Merck) alumina and the crude product (10; R^1 = R^2 = H) was dissolved in tetrahydrofuran and treated with methyl-lithium as described for (10; R^1 = Me, R^2 = H). The intermediate imine was hydrolysed with 2M-hydrochloric acid to afford 11-demethylellipticine as pale yellow crystals [overall yield from (7; R^1 = R^2 = H), 28%], m.p. 275—277° (lit.,[12] 276°), *m/e* 232 (M^+) and 208 (base); $\lambda_{max.}$ (0.1M-HCl in 85% EtOH) 238 (ε 27 000), 248sh (25 000), 270sh (20 000), 307 (73 000), and 350 nm (7 000); $\nu_{max.}$ 1 605 and 1 250 cm^{-1} (Found: C, 82.8; H, 5.1; N, 12.0. Calc. for $C_{17}H_{12}N_2$: C, 82.7; H, 5.2; N, 12.1%).

5,6-*Methylenedioxy*-3-[1-(*3-pyridyl*)*ethyl*]*indole* (12; R = Ac).—(*a*) 5,6-Methylenedioxyindole [10] was combined with the chloropyridine (8; X = Cl) as described for the preparation of (7; R^1 = Me, R^2 = H). However, since we had a limited quantity of the indole, a mixture of ethylmagnesium bromide, the indole, and the chloropyridine was used, in the molar ratios 1 : 1 : 1. The product was obtained as white *prisms* (12%), m.p. 182—183° (from ethanol); *m/e* 266 (M^+) and 251 (base); $\nu_{max.}$ 3 100, 1 590, 1 580, 1 300, and 1 030 cm^{-1}; δ [$CDCl_3$–6% $(CD_3)_2SO$] 10.17br (1 H, s, NH), 8.52 (1 H, s, pyridyl 2-H), 8.37 (1 H, d, *J* 6 Hz, pyridyl 6-H), 7.54 (1 H, m, pyridyl 4-H), 7.15 (1 H, m, pyridyl 5-H), 6.94 (1 H, s, indole 2-H), 6.82 (1 H, s, indole 7-H), 6.6 (1 H, s, indole 4-H), 5.81 (2 H, s, O·CH_2·O), 4.25 (1 H, q, *J* 9 Hz, C*H*·CH_3), and 1.63 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 72.1; H, 5.4; N, 10.7. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%).

(*b*) The reaction was repeated, but in dry tetrahydrofuran, and the mixture was heated under reflux for 1 h. The yield of product was only 6%.

(*c*) The experiment was repeated with methyl-lithium instead of ethylmagnesium bromide. The yield of final product was 3%.

* We thank Miss M. McCartney, British Cellophane Ltd., Bridgwater, for this experiment.

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1-Acetyl-5,6-methylenedioxy-3-[1-(3-pyridyl)ethyl]indole (12; R = Ac).—The indole (12; R = H) was converted into the acetyl derivative as described for the unsubstituted compounds, to give white *crystals* (93%), m.p. 160—161° (from ethanol); *m/e* 308 (M^+), 266, and 251 (base); $\nu_{max.}$ 1 690 and 1 600 cm^{-1}; δ 8.6 (1 H, s, pyridyl 2-H), 8.38 (1 H, d, *J* 6 Hz, pyridyl 6-H), 7.92 (1 H, s, indole 7-H), 7.5 (1 H, m, pyridyl 4-H), 7.14 (1 H, m, pyridyl 5-H), 7.08 (1 H, s, indole 2-H), 6.5 (1 H, s, indole 4-H), 5.9 (2 H, s, O·CH_2·O), 4.1 (1 H, q, *J* 9 Hz, C*H*·CH_3), 2.6 (3 H, s, Ac), and 1.65 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 70.1; H, 5.3; N, 9.0. $C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.2; N, 9.1%).

3-[1-(1-Acetyl-5,6-methylenedioxyindol-3-yl)ethyl]pyridine-4-carbonitrile (13).—The indole (12; R = Ac) was converted, by a series of steps similar to those already described, into the title *compound*, which was obtained as a white crystalline solid, after chromatography on neutral alumina and elution with chloroform [yield from (12; R = H), 79%]; m.p. 196—197°; *m/e* 333 (M^+), 291, 276 (base), and 251; $\nu_{max.}$ 2 200, 1 690, and 1 590 cm^{-1}; δ 8.53 (1 H, d, *J* 6 Hz, pyridine 6-H), 8.5 (1 H, s, pyridine 2-H), 7.9 (1 H, s, indolyl 7-H), 7.23 (1 H, d, *J* 6 Hz, pyridine 5-H), 7.18 (1 H, s, indolyl 4-H), 6.43 (1 H, s, indolyl 2-H), 5.9br (2 H, s, O·CH_2·O), 4.55 (1 H, q, *J* 8 Hz, C*H*·CH_3), 2.63 (3 H, s, Ac), and 1.78 (3 H, d, *J* 7 Hz, CH·C*H*$_3$) (Found: C, 68.7; H, 4.6; N, 12.5. $C_{19}H_{15}N_3O_3$ requires C, 68.5; H, 4.5; N, 12.6%).

8,9-Methylenedioxyellipticine (14).—The nitrile (13), after elution in chloroform through a basic alumina column, was treated with an excess of methyl-lithium, and the product was worked up in the usual manner to give the corresponding imine. This was transformed into the title compound by heating in 2M-hydrochloric acid for 30 min, basifying with sodium hydrogen carbonate and extracting with chloroform. Evaporation of the organic phase under reduced pressure furnished the yellow 8,9-methylenedioxyellipticine [65% from (12; R = H)], m.p. 330—333° (decomp.) (from ethanol) (lit.,[3i] 333°); *m/e* 290 (M^+, base), 275, 261, 251, and 231; $\nu_{max.}$ 3 300, 1 620, 1 580, and 1 020 cm^{-1}; $\lambda_{max.}$ 213 (ε 40 000), 229 (38 200), 249 (28 500), 273sh (45 400), 283 (58 000), 316 (72 500), and 246 nm (15 500); δ [$(CD_3)_2SO$] 11.15 (1 H, s, NH), 9.72br (1 H, s, 1-H), 8.48 (1 H, dd, *J* 8 and 2 Hz, 3-H), 7.97 (2 H, m, 4- and 10-H), 7.2 (1 H, s, 7-H), 6.2 (2 H, s, O·CH_2·O), 3.22 (3 H, s, CH_3), and 2.79 (3 H, s, CH_3) (Found: C, 74.4; H, 5.0; N, 9.6. Calc. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.9; N, 9.7%).

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SYNTHESIS OF THE INDOLO[2',2':3,4]PYRIDO[1,2-b][2,7] NAPHTHYRIDINONE ALKALOID NAUCLEFINE AND ITS RING-E ISOMERS

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Synthesis of the Indolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridinone Alkaloid Nauclefine and its Ring-E Isomers

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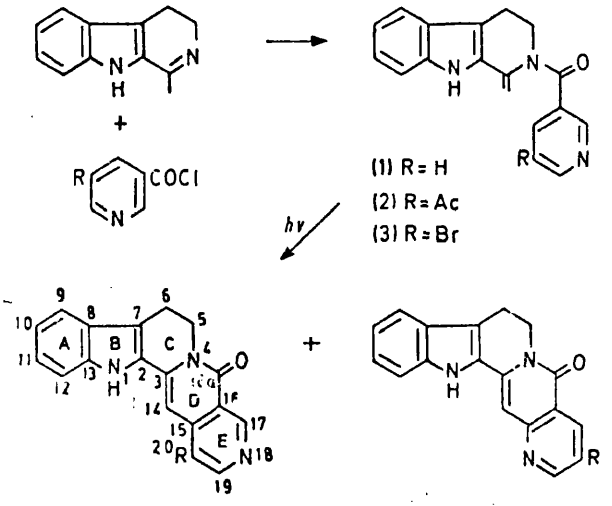
Nauclefine has been reported to be the only product from the photocyclisation of the enamide derived from harmalan and nicotinoyl chloride. Re-investigation has shown, however, that two compounds are formed: the alkaloid and an isomer in which cyclisation to the 2-position of the pyridyl unit has occurred. These components have been separated and the remaining ring-E isomers have been synthesized. ^{1}H and ^{13}C n.m.r. data for these structures are analysed.

THE alkaloid nauclefine (parvine †) (4) has been synthesised by the route outline in the Scheme.[1,2] However,



(1) R = H
(2) R = Ac
(3) R = Br

(4) R = H
(5) R = Ac
(6) R = Br
(7) R = CH(OH)Me

(8) R = H
(9) R = Ac
(10) R = Br

SCHEME

because of the two possible modes of photocyclisation of the enamide (1)[3] it was surprising that nauclefine appeared to be the sole product of this reaction. When the photolysis was repeated, t.l.c. (alumina) showed only one spot, identical in behaviour with the natural product (R_F 0.75 in acetone; 0.62 in methanol), and a similar correlation of mass, i.r., and u.v. spectra was apparent. The ^{1}H n.m.r. spectrum had been recorded previously for a recrystallised sample of the photolysis product,[2] but this time when the spectrum of the crude material was determined, the presence of a minor component (10—12%) was revealed. This conclusion was supported by ^{13}C n.m.r. data (see later).

The isomers were separated by column chromatography with dichloromethane–methanol mixtures (which also allows the recognition of two components on t.l.c.), affording pure nauclefine and isonauclefine (8). ^{1}H N.m.r. assignments for ring E in each of the two compounds are summarized in Table 1. Chemical shifts and coupling constants for solutions in $(CD_3)_2SO$ agree well with values calculated for model systems,[4] but in trifluoroacetic acid solution the signals for H-17 and -19 in nauclefine appear as a doublet and a triplet, respectively.

This effect has been noted previously in isoquinolines [5] and is presumably due to *N*-protonation. The signals of isonauclefine in trifluoroacetic acid solution do not show this increased multiplicity; interestingly, nauclefine readily forms a methiodide whereas its isomer does not. The H-17 resonance of nauclefine is only slightly changed in trifluoroacetic acid solution, with respect to its position in $(CD_3)_2SO$ (+0.24 p.p.m.), but the H-17 signal in isonauclefine undergoes a considerable downfield shift (+0.72 p.p.m.) and the H-19 resonance is actually moved upfield (−0.12 p.p.m.). These results suggest that quaternization of the ring-E nitrogen atom in isonauclefine is not favoured, possibly because of steric interaction with the *peri* H-14, and thus in trifluoroacetic acid solution protonation of the oxygen atom of the amide carbonyl group may occur preferentially.

Au *et al.*[6] note that angustoline is a strong base which is protonated even by acetic acid. For example, dropwise addition of acetic acid to a methanolic solution of the alkaloid causes a progressive, and ultimately complete, shift of the longest wavelength absorption band in the electronic spectrum from 395 to 439 nm. These workers propose that the conjugate acid, formed by protonation of the ring-E nitrogen atom, is stabilized through resonance with the indolic nitrogen atom. Such stabilization is possible with both the similarly formed conjugate acids of nauclefine and isonauclefine but, significantly, whereas the electronic spectrum of the former is slowly changed by dropwise addition of acetic acid ($\lambda_{max.}$ 391 to 448 nm) that of isonauclefine is not. Only in 75% acetic acid in methanol does an absorption band start to appear at 445 nm, and even in glacial acetic acid this band does not replace the absorption maxima of the free base at 362 and 380 nm,‡ and

† The use of this name should be discontinued since Pousset's study [1] has precedence over ours.[2]

‡ The electronic spectrum of bromoisonauclefine is not affected by the addition of acetic acid.

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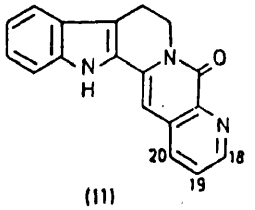
[6] T. Y. Au, H. T. Cheung, and S. Sternhell, *J.C.S. Perkin I*, 1973, 13.

extinction coefficient measurements indicate that *ca.* 70% of the unprotonated form is present in this solvent.

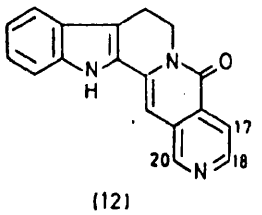
Cyclisation involving the γ-carbon atom of the pyridyl group and the exocyclic methylene group in the enamide precursor (1) is favoured electronically, but Ninomiya [3a] noted in the synthesis of angustoline that the enamide (2), in which the pyridine unit bears a relatively bulky 3-substituent, affords the isomers (5) and (9) in a molar ratio of 4 : 1.

In an attempt to increase the yield of isonauclefine the bromoenamide (3) was irradiated; it was hoped that after separation of the products the bromo-substituent in (10) might be removed by hydrogenolysis. However, although the isomers (6) and (10) were obtained in a molar ratio of 2.4 : 1 and were separated by column chromatography, all attempts failed to remove the bromine atom in either.

In order to assist in the interpretation of the ^1H and ^{13}C n.m.r. spectra of nauclefine and isonauclefine, the isomers (11) and (12) were prepared, by photocyclisation

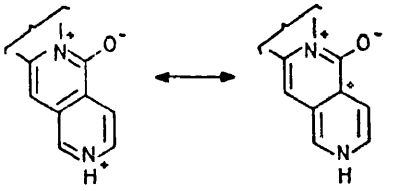


(11)



(12)

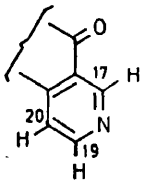
of the enamides derived from harmalan with picolinoyl and isonicotinoyl chloride, respectively. The electronic absorption spectra of (11) and (12) are little changed by the addition of acetic acid. Here, however, the adverse resonance effects implicit in the *N*-protonated forms might be expected to destabilize them; see, for example, part structure (13). In line with this conclusion, (11) does not form a methiodide even under forcing conditions, but perversely the 19-aza-isomer (12) is readily converted into its methiodide salt. In the first case, however, the carbonyl group at C-16a imposes an additional steric constraint to quaternary salt formation.



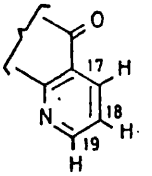
(13)

TABLE 1

Chemical shifts (δ values; MeSi standard) and coupling constants (*J*/Hz) for ring-E protons of nauclefine (A) and isonauclefine (B) in $(CD_3)_2SO$ and in $CF_3{\cdot}CO_2H$



(A)



(B)

	(A)			(B)	
	$(CD_3)_2SO$	$CF_3{\cdot}CO_2H$		$(CD_3)_2SO$	$CF_3{\cdot}CO_2H$
H-17	9.32br (s)	9.56 (d, *J* 6)	H-17	8.54 (dd, $J_{17,18}$ 8, $J_{17,19}$ 2)	9.26 (d, *J* 6)
H-19	8.66br (d)	8.36 (t, *J* 6)	H-18	*ca.* 7.4	7.70 (t, *J* 6)
H-20	*ca.* 7.6	7.83 (d, *J* 6)	H-19	8.90 (dd, $J_{18,19}$ 5, $J_{17,19}$ 2)	8.78 (d, *J* 6)

Provisional ^{13}C n.m.r. assignments for nauclefine and its ring-E isomers are summarized in Table 2. These allocations are based upon chemical shift values expected for specific types of carbon atom,[4b,7,8] and off-resonance ^1H decoupling studies.

TABLE 2

Provisional ^{13}C n.m.r. assignments (δ values; $MeSi_4$ standard) for nauclefine and its ring-E isomers

Carbon no.	Structures (4) †	(8) †	(11) ‡	(12) §
3	136.93	135.70	§	134.14
5	39.96	39.96	45.29	39.50
6	19.10	19.11	20.72	19.04
7	114.51	113.60	114.06	113.02
8	127.38	127.64	127.38	127.77
9	119.71	119.32	120.49	119.19
10	124.26	123.94	123.42	123.74
11	119.51	119.52	121.73	119.58
12	111.78	111.72	110.91	111.65
13	138.36	138.17	138.16	138.10
14	96.83	100.28	§	96.12
15	121.35	152.79	126.37	128.61
16	125.23	120.10	141.87	130.82
16a	160.85	161.50	§	160.20
17	150.77	135.50		125.30
18		121.01	147.5	145.25
19	150.32	154.81	131.21	
20	118.73		143.30	149.22

† $(CD_3)_2SO$ as solvent. ‡ $CF_3{\cdot}CO_2H$ as solvent. § Masked by solvent absorption.

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EXPERIMENTAL

U.v. spectra were recorded for solutions in methanol; i.r spectral data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at 100 MHz with tetramethylsilane (TMS) as internal standard. TMS was also used as internal reference for ^{13}C n.m.r. spectra. Column chromatography was conducted with Merck neutral grade alumina.

Nauclefine (4) *and Isonauclefine* (8).—The enamide (1) (400 mg), prepared from nicotinoyl chloride and harmalan,[1,2] in methanol (800 cm^3), was irradiated in a Hanovia reactor with ' soft ' u.v. light. After 20 h the solvent was removed and the brown amorphous residue subjected to spectroscopic and chromatographic analysis; δ[$(CD_3)_2SO$] 9.32br (s) and 8.9 (q) (integral ratio 1 : 0.09), and 8.66br (s) and 3.54 (q) (integral ratio 1 : 0.09). Column chromatography and elution with 3% methanol in dichloromethane gave *isonauclefine* {8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one*} (8), m.p. >350 °C, *m/e* 287 (M^+, 100%), 286 (85), 272 (12), and 258 (13), $\lambda_{max.}$ 362 and 380 nm, $\nu_{max.}$ 3 240, 1 650, 1 606, and 1 593 cm^{-1}, δ[$(CD_3)_2SO$] 11.76 (1 H, s, NH), 8.90 (1 H, dd, *J* 5 and 2 Hz, 19-H), 8.54 (1 H, dd, *J* 8 and 2 Hz, 17-H), 7.7—7.0 (5 H, m), 4.4 (2 H, t, *J* 7 Hz, 5-H_2), and 3.12 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.2; H, 4.5; N, 14.2. $C_{18}H_{13}N_3O$ requires C, 75.2; H, 4.6; N, 14.6%).

Elution with 5% methanol in dichloromethane afforded nauclefine, identical (m.p. and mixed m.p. 298—299 °C) with the natural alkaloid (lit.,[2] m.p. 293—294 °C); methiodide, m.p. 330 °C (lit.,[2] 330 °C), *m/e* 287 (M^+, 100%), 286 (80), 272 (12), and 258 (13%), $\lambda_{max.}$ 372 and 391 nm, $\nu_{max.}$ 3 180, 1 650, 1 615, and 1 597 cm^{-1} (Found: C, 75.2; H, 4.4; N, 14.3%).

2-(5-*Bromonicotinoyl*)-1,2,3,4-*tetrahydro*-1-*methylene*-β-*carboline* (3).—*Compound* (3), from harmalan and 5-bromonicotinoyl chloride, had m.p. 158 °C; $\nu_{max.}$ 3 330, 1 650, 1620, and 1 580 cm^{-1}, δ_H($CDCl_3$) 8.93 (1 H, s, NH), 8.66 (1 H, dd, *J* 2.2 and 0.3 Hz), 8.51 (1 H, dd, *J* 2 and 0.3 Hz), 7.98 (1 H, dd, *J* 2.2 and 2 Hz), 5.03 (1 H, d, *J* 2.2 Hz), 4.32 (1 H, d, *J* 2.2 Hz), 4.2 (2 H, t, *J* 6 Hz), and 3.0 (2 H, t, *J* 6 Hz), δ_C [$(CD_3)_2SO$] 136.2 (C-3), 44.65 (C-5), 22.96 (C-6), 113.67 (C-7), 128.68 (C-8), 119.26 (C-9), 124.20 (C-10), 120.36 (C-11), 111.33 (C-12), 138.3 (C-13), 103.33 (C-14), 137.45 (C-15), 126.7 (C-16), 166.18 (C-16a), 151.75 (C-17), 146.81 (C-19), and 133.4 (C-20) (Found C, 58.6; H, 3.7; N, 11.2. $C_{18}H_{14}BrN_3O$ requires C, 58.7; H, 3.8; N, 11.4%).

20-*Bromonauclefine* (6) *and* 18-*Bromoisonauclefine* (10).—The enamide (3) (0.8 g) was irradiated in the usual way and the product chromatographed. Elution with dichloromethane gave 18-*bromoisonauclefine* (50 mg), m.p. >350 °C, *m/e* 367, 365 (M^+, 68%), 364 (40%), 257 (14), 215 (21), and 125 (100), $\lambda_{max.}$ 260, 360, and 380 nm, $\nu_{max.}$ 3 200, 1 640, 1 600, and 1 580 cm^{-1}, δ [$(CD_3)_2SO$] 11.3 (1 H, s, NH), 8.88 (1 H, d, *J* 2.5 Hz, 17-H), 8.58 (1 H, d, *J* 2.5 Hz, 20-H), 7.7—7.0 (4 H, m), 7.18 (1 H, s, 14-H), 4.4 (2 H, t, *J* 7 Hz, 5-H_2), and 3.1 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 59.2; H, 3.5; N, 4.1. $C_{18}H_{12}BrN_3O$ requires C, 59.0; H, 3.3; N, 4.4%). With 1% methanol in dichloromethane, 20-*bromonauclefine* (6) 120 mg), m.p. >350°, was obtained, *m/e* 367, 365 (68%), 364 (40), 257 (14), 215 (21), and 125 (100), $\lambda_{max.}$ 240, 254, 295, 306, 373, and 403 nm, $\nu_{max.}$ 3 200br, 1 660, 1 635, and 1 600 cm^{-1}, δ [$(CD_3)_2SO$] 12.0 (1 H, s, NH), 9.23 (1 H, s, 17-H), 8.84 (1 H, s, 20-H), 7.7—7.0 (4 H, m), 7.12 (1 H, s, 14-H), 4.38 (2 H, t, *J* 7 Hz, 5-H_2), and 3.17 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 59.3; H, 3.3; N, 4.1%).

Nauclefine Ring-E *Isomers* (11) *and* (12).—The *isomer* (11) {8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[2,1-g][1,7]*naphthyridin*-5(7H)-*one*} was obtained by irradiation of the enamide from picolinoyl chloride and harmalan (this enamide was not purified, but used directly); it had m.p. 250—251 °C (decomp.) (from methanol), *m/e* 287 (M^+, 100%), 286 (85), 272 (12), 258 (13); $\lambda_{max.}$ 354 and 375sh nm, $\nu_{max.}$ 3 210, 1 650, 1 620, 1 605, and 1 595 cm^{-1}, δ [$(CD_3)_2SO$] 11.76 (1 H, s, NH), 8.76br (1 H, s, 18-H), 8.08 (1 H, d, *J* 8 Hz, 20-H), 7.66 (1 H, m, 19-H), 7.6—7.0 (4 H, m), 7.04 (1 H, s, 14-H), 4.44 (2 H, t, *J* 7 Hz, 5-H_2), and 3.12 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.2; H, 4.5; N, 14.3. $C_{18}H_{13}N_3O$ requires C, 75.2; H, 4.6; N, 14.6%). The *isomer* (12) {8,13-*dihydroindolo*-[2′,3′ : 3,4]*pyrido*-[1,2-b][2,6]*naphthyridin*-5(7H)-*one*} was prepared in similar manner from the enamide from isonicotinoyl chloride and harmalan {the *enamide* had m.p. 206 °C, δ [$(CD_3)_2SO$] 11.2 (1 H, s), 8.6 (2 H, dd, *J* 4.25 and 1.5 Hz), 7.7—6.9 (4 H, m), 7.32 (2 H, dd, *J* 4.25 and 1.5 Hz), 5.36br (1 H, s, *J* <1 Hz), 4.54br (1 H, s, *J* <1 Hz), 4.06 (2 H, t, *J* 6 Hz), 2.92 (2 H, t, *J* 6 Hz) (Found: C, 74.7; H, 5.55; N, 13.9. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.0%)}. After removal of the solvent used in the irradiation experiment, the crude isomer (12) was purified by elution (4% methanol in dichloromethane) through a silica column to afford yellow prisms, m.p. >350 °C, *m/e* 287 (M^+, 100%), 286 (63), 272 (12), and 258 (13); $\lambda_{max.}$ 353 and 390sh nm, δ [$(CD_3)_2SO$] 11.6 (1 H, s, NH), 9.02 (1 H, s, 20-H), 8.58 (1 H, d, *J* 5 Hz, 17-H), 8.02 (1 H, d, *J* 5 Hz, 18-H), 7.7—7.0 (4 H, m), 7.14 (1 H, s, 14-H), 4.4 (2 H, d, *J* 7 Hz, 5-H_2), and 3.08 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.1; H, 4.6; N, 14.5%); methiodide, m.p. >350 °C, δ [$(CD_3)_2SO$] 11.98 (1 H, s, NH), 9.68 (1 H, s, 20-H), 8.67 (1 H, d, *J* 6 Hz, 17-H), 8.53 (1 H, d, *J* 6 Hz, 18-H), 7.7—7.0 (4 H, m), 7.16 (1 H, s, 14-H), 4.44 (2 H, t, *J* 6 Hz, 5-H_2), and 3.16 (2 H, t, *J* 6 Hz, 6-H_2).

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